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Proposed Registration Decision PRD2018-14

Thiamethoxam, Actara 25WG Insecticide, Actara 240SC Insecticide, and other related end-use products

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Table of Contents

Overview 1
Background 1
Registration Status of Thiamethoxam 2
Proposed Registration Decision for Thiamethoxam 4
What Does Health Canada Consider When Making a Registration Decision? 6
What Is Thiamethoxam? 6
Health Considerations 6
Environmental Considerations 9
Value Considerations 9
Measures to Minimize Risk 10
Conclusion 11
Next Steps 11
Science Evaluation 13
1.0 The Active Ingredient, Its Properties and Uses 13
1.1 Identity of the Active Ingredient 13
1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product 13
1.3 Directions for Use 15
1.4 Mode of Action 15
2.0 Methods of Analysis 16
2.1 Methods for Analysis of the Active Ingredient 16
2.2 Method for Formulation Analysis 16
2.3 Methods for Residue Analysis 16
3.0 Impact on Human and Animal Health 16
3.1 Toxicology Summary 16
3.2 Determination of Acute Reference Dose 25
3.3 Determination of Acceptable Daily Intake 26
3.4 Occupational and Residential Risk Assessment 26
3.4.1 Toxicological Endpoints 26
3.4.2 Occupational Exposure and Risk 27
3.4.3 Residential Exposure and Risk Assessment 29
3.5 Food Residues Exposure Assessment 29
3.5.1 Residues in Plant and Animal Foodstuffs 29
3.5.2 Dietary Risk Assessment 30
3.5.3 Aggregate Exposure and Risk 30
3.5.4 Maximum Residue Limits 30
3.5.5 Concentrations in Drinking Water 30
4.0 Impact on the Environment 31
4.1 Fate and Behaviour in the Environment 31
4.2 Environmental Risk Characterization 32
4.2.1 Risks to Terrestrial Organisms 33
4.2.2 Risks to Aquatic Organisms 34
4.2.3 Incident Reports 34
5.0 Value 35

6.0 Pest Control Product Policy Considerations 35
6.1 Toxic substance Management Policy Considerations 35
6.2 Formulants and Contaminants of Health or Environmental Concern 35
7.0 Summary 36
7.1 Human Health and Safety 36
7.2 Environmental Risk 37
7.3 Value 37
8.0 Proposed Regulatory Decision 37
List of Abbreviations 39
Appendix I Tables and Figures 43
Table 1 Residue Analysis 43
Table 2 Select Thiamethoxam Metabolites 43
Table 3 Toxicology Profile of Technical Thiamethoxam (CGA 293343) 43
Table 4 Toxicity Profile of End-Use Products (Actara 240SC Insecticide and Actara 25WG Insecticide) 59
Table 5 Toxicology Reference Values for Use in Human Health Risk Assessment for Thiamethoxam 60
Table 6 Mixer/Loader/Applicator Risk Assessment 62
Table 7 Post-application Risk Assessment – Pome Fruit Orchards 62
Table 8 Integrated Food Residue Chemistry Summary 63
Table 9 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment 69
Appendix II 71
References 73

Overview

Background

History of the use pattern for foliar and soil uses of thiamethoxam

In October 2006, the major new uses of terrestrial food and feed crops (Use-Site Categories[1] (USCs) 13 and 14) were approved for Thiamethoxam Technical (Reg. No. 26665) as a conditional registration. The end-use products associated with these uses were Actara 25WG Insecticide and Actara 240SC Insecticide. Following the standard process for conditional registrations, the Pest Management Regulatory Agency (PMRA) subsequently published an evaluation report, ERC2007-01, *Thiamethoxam*, outlining the science risk assessment for the use of these products as foliar treatments for pome fruits and potatoes, as well as in-furrow application for potatoes. According to the former conditional registration regulations,[2] consultation on USCs 13 and 14 would have been required when a proposed decision to convert the conditional registrations to full registrations was issued, or when the conditional registrations were renewed, whichever occurred first. With the continuation of the conditional registration in 2008, that consultation should have taken place. However, due to an administrative oversight, the consultation process did not occur. This oversight is being rectified in this consultation document.

Since the publication of ERC2007-01, other end-use products containing thiamethoxam, Endigo Insecticide and Minecto Duo 40WG, have been registered for USCs 13 and 14. Subsequently, the major new uses of ornamentals outdoor (USC 27) and greenhouse food crops (USC 5) were added to Thiamethoxam Technical, under the minor use program, and Flagship Insecticide was later registered based on the Actara 25WG Insecticide precedent. All these end-use products are listed in Table 1 below.

Current consultation

Health Canada is consulting the public under section 28(1)(a) of the *Pest Control Products Act* for the major new uses of foliar and soil application to terrestrial food and feed crops that were conditionally registered in 2006. As such, this proposed registration decision document summarizes the risk assessment of the original use pattern for the two end-use products, Actara 25WG Insecticide and Actara 240SC Insecticide, which would have been consulted on in 2008 but for the administrative oversight.

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1 Details at: https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/registrants-applicants/product-application/use-site-category-daco-tables/definitions-conventional-chemical-pesticides.html

2 Sections 14, 15 and 16(2) of the Pest Control Products Regulations, repealed on 30 November 2017.

In addition, the PMRA considers it in the public interest to consult on the proposed registration decisions to grant a three-year registration to Endigo Insecticide, Flagship Insecticide and Minecto Duo 40WG. These uses were approved under User Requested Minor Use Label Expansions (URMULE),[3] or based on precedent products. These consultations are carried out under 28(1)(c) of the *Pest Control Products Act* in light of, and in response to the growing public interest in the registration status of the neonicotinoid insecticides.

All products subject to consultation in this document are listed in Table 1.

Table 1 List of products subject to consultation in this document

Product Name	Reg. No.	Legislative authority under which consultation is being conducted[4]
Thiamethoxam Technical USCs 13 and 14	26665	28(1)(a)
Actara 240SC Insecticide	28407	28(1)(a)
Actara 25WG Insecticide	28408	28(1)(a)
Thiamethoxam Technical USCs 5 and 27	26665	28(1)(c)
Endigo Insecticide	30404	28(1)(c)
Flagship Insecticide	30723	28(1)(c)
Minecto Duo 40WG	30900	28(1)(c)

Registration Status of Thiamethoxam

Fully registered uses

Thiamethoxam Technical (Reg. No. 26665) is fully registered in Canada for use in gel bait insecticides for ant control (USC 20 - Structures).

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3 https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/growers-commercial-users/user-requested-minor-use.html

4 28 (1) The Minister shall consult the public and federal and provincial government departments and agencies whose interests and concerns are affected by the federal regulatory system before making a decision, (a) to grant or deny an application ... (c) about any other matter if the Minister considers it in the public interest to do so.

Conditionally registered uses and data requirements

Thiamethoxam Technical and its associated end-use products used as seed treatments and for foliar and soil applications are conditionally registered in Canada. Refer to PRD2017-18, *Thiamethoxam* for the conditions and proposal associated with the seed treatments uses (USC 10). Refer to PRD2018-13, *Thiamethoxam and Mainspring X Insecticide* for the conditions and proposal associated with the greenhouse non-food uses (USC 6).

For foliar and soil uses discussed in this document, both pollinator and non-pollinator data requirements were initially required in ERC2007-01.

1) List of non-pollinator data required as a condition of registration, as found in ERC2007-01:

DACO 8.2.1	(N-octanol-water partitioning coefficient for the major transformation product CGA-355190)
DACO 8.2.2.1	(Analytical methodology for soil)
DACO 8.2.2.3	(Analytical methodology for water)
DACO 8.2.2.4	(Analytical methodology for biota)
DACO 9.3.4	(Toxicity of the major transformation products CGA-355190, CGA- 353042, NOA-404617 and NOA-407475 to an aquatic invertebrate (*Chironomus* sp.)
DACO 9.8.4	(Toxicity of Thiamethoxam to terrestrial plants (plant screening data))

For the outcome of the review of the information provided to fulfil the above conditions of registration, refer to Section 4.0 of this document.

2) List of pollinator data, as revised and found in the most recent section 12 notices,[5] as a condition of registration currently associated with these products.

DACO: 8.5

Title:	Fate of thiamethoxam and the transformation product clothianidin in plants, including concentrations in nectar and pollen.
Required data:	A study which determines the concentration of thiamethoxam and clothianidin in nectar and pollen of plants (plant fate study).

DACO:	9.2.4.3
Title:	Hive Study (field)
Required data:	The new study must follow currently accepted guidelines and address concerns regarding toxicity of thiamethoxam and the transformation.

[5] https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/public/protecting-your-health-environment/conditional-registrations.html

For the outcome of the review of the information provided to fulfil the above conditions of registration, refer to Section 4.2.1 of this document.

Re-evaluation and special review of thiamethoxam

The re-evaluation of thiamethoxam to assess risks to pollinators was announced in 2012 (Re-evaluation Note REV2012-02, *Re-evaluation of Neonicotinoid Insecticides*). This re-evaluation was initiated to assess the potential risk to pollinators in light of international updates to the pollinator risk assessment framework, including information requirements. Data obtained from published literature as well as data received from the registrants, including the information that were required to fulfill the conditions of registration under section 12 (DACOs 8.5 and 9.2.4.3), were considered in the re-evaluation assessment.

In addition, the PMRA announced in 2016 the initiation of a special review to evaluate the impact of thiamethoxam on aquatic invertebrates (Re-evaluation Note REV2016-17, *Initiation of Special Reviews: Potential Environmental Risk to Aquatic Invertebrates Related to the Use of Clothianidin and Thiamethoxam*).

Health Canada has conducted an assessment of pollinator risk for thiamethoxam, as well as a special review to evaluate the impact of thiamethoxam on aquatic invertebrates. A Proposed Re-evaluation Decision and a Proposed Special Review Decision have been published:

- PRVD2017-24, *Thiamethoxam and Its Associated End-use Products: Pollinator Re-Evaluation*, summarizes the science evaluation with regards to the potential risks posed by thiamethoxam to pollinators in Canada, as well as proposes strategies to reduce the risks to these pollinators.

- PSRD2018-02, *Special Review of Thiamethoxam Risk to Aquatic Invertebrates: Proposed Decision for Consultation*, summarizes the science evaluation with regards to the potential risks posed by thiamethoxam to aquatic invertebrates in Canada, as well as proposes strategies to reduce the risks to these organisms.

The continued registration of the products in Table 1 is affected by these re-evaluation and special review proposals, and as a result, some uses are currently proposed for cancellation. The continued registration of the products in Table 1 and of USCs 5, 13, 14, and 27 of the technical active ingredient thiamethoxam will be subject to the outcomes of the final decisions pertaining to the re-evaluation and special review of thiamethoxam.

Proposed Registration Decision for Thiamethoxam

With respect to foliar and soil uses of thiamethoxam, Health Canada's PMRA, under the authority of section 8 of the *Pest Control Products Act*, is proposing a three-year registration for the sale and use of the technical grade active ingredient thiamethoxam and the end-use products listed in Table 1. These consultations are carried out under either 28(1)(a) or under 28(1)(c) of the *Pest Control Products Act* (see Table 1). Note that consultations under 28(1)(c) are not subject to subsection 35(1) of the *Pest Control Products Act*.

An evaluation of available scientific information found that:

- For USC 5 (greenhouse peppers), the product has value and presents an acceptable risk to human health and the environment, when used according to the proposed conditions of registration, which include amendments to the label. To address potential risks to pollinators and aquatic invertebrates, amendments to the registration of the end-use product have been proposed.

- For USCs 13, 14 and 27, for the time period of the registration, the products have value and present an acceptable risk to human health and the environment, when used according to the proposed conditions of registration, which include amendments to the label. To address potential risks to pollinators and aquatic invertebrates, some uses are currently proposed for cancellation and amendments to the registrations of the end-use products have been proposed.

The continued registration of the products in Table 1 will be subject to the outcomes of the final decisions pertaining to the re-evaluation and special review of thiamethoxam.

Before making a final registration decision on Thiamethoxam, Actara 25WG Insecticide, Actara 240SC Insecticide, and other related end-use products, the PMRA will consider any comments received from the public in response to this consultation document.[6] The PMRA will then publish a Registration Decision[7] on Thiamethoxam, Actara 25WG Insecticide, Actara 240SC Insecticide, and other related end-use products, which will include the decision, the reasons for it, a summary of comments received on the proposed registration decision and Heath Canada's response to these comments. In addition, the confidential test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

This Overview describes the key points of the evaluation of thiamethoxam on the original use pattern approved for USCs 13 and 14, while the Science Evaluation and tables in Appendix I provide detailed technical information on the human health, environmental and value assessments of thiamethoxam and the end-use products Actara 25WG Insecticide and Actara 240SC Insecticide. For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document. Also, further information on the use expansions to USCs 5 and 27 can be found in Appendix II of this document.

Validity period of conditional registrations

In order to complete the consultations, the validity periods of the products listed in Table 1 have been extended until 31 December 2020. This extension is also applicable to the USCs 5, 13, 14 and 27 of Thiamethoxam Technical (Reg. No. 26665). This extension was granted under 14(7)[8]

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6 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

7 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

8 SOR/2017-91, section 11

of the former Pest Control Products Regulations, to carry out the consultation on the proposed registration decisions with respect to these products.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions.[9] The *Pest Control Products Act* also requires that products have value[10] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk. When special review or re-evaluation decisions affect the registration of a product, the effective date of the amendment or cancellation may also be delayed as long as there is no suitable alternative and the risk is acceptable during that time period.[11]

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (for example, children) as well as organisms in the environment. These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides section of Canada.ca.

What Is Thiamethoxam?

Thiamethoxam is the active ingredient in the commercial class products Actara 25WG Insecticide and Actara 240SC Insecticide. Actara 240SC Insecticide is applied using in-furrow application equipment on potatoes. Actara 25WG Insecticide is applied using foliar application equipment on pome fruits. Thiamethoxam moves through the leaf surface and the translocation system of the plant, affecting the insects through contact and ingestion.

Health Considerations

Can Approved Uses of Thiamethoxam Affect Human Health?

Actara 240SC Insecticide and Actara 25WG Insecticide, containing thiamethoxam, are unlikely to affect your health when used according to label directions.

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9 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

10 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "... the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

11 Subsection 21(3) of the *Pest Control Products Act*.

Potential exposure to thiamethoxam may occur through the diet (food and water) or when handling and applying the products. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher (and often much higher) than levels to which humans are normally exposed when using pesticide-containing products according to label directions.

In laboratory animals, the technical grade active ingredient thiamethoxam was moderately acutely toxic via the oral route and of low toxicity via the dermal and inhalation routes of exposure. It was minimally irritating to eyes, non-irritating to skin, and it did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statement "WARNING POISON" are required on the label.

Actara 240SC Insecticide was of low acute toxicity via the oral and dermal routes of exposure. It was slightly acutely toxicity via the inhalation route. Actara 240SC Insecticide was non-irritating to eyes and slightly irritating to skin. it did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statement "CAUTION POISON" are required on the product label.

Actara 25WG Insecticide was of low acute toxicity via the oral, dermal, and inhalation routes of exposure. It was mildly irritating to eyes and slightly irritating to skin. Actara 25WG Insecticide did not cause an allergic skin reaction. Based on these findings, the signal word and hazard statement "CAUTION EYE IRRITANT" are required on the product label.

Health effects in animals given repeat doses of thiamethoxam over long periods of time included effects on the liver, kidneys, testes and nervous system. There was no evidence to suggest that thiamethoxam damaged genetic material, and it did not cause cancer in rats. Thiamethoxam did produce liver tumours in mice; however, the process of tumour formation is not expected to occur in humans due to differences in metabolism. In animal reproductive toxicity tests, adverse effects on the sperm and testes of offspring were observed at dose levels that did not have health effects in the mother, indicating that the young were more sensitive to thiamethoxam than the adult animal. In additional studies in which pregnant animals were given thiamethoxam, reduced brain weight and changes in brain measurements were observed in offspring at dose levels which produced minimal effects on the mother, again suggesting sensitivity of the young. The risk assessment protects against the effects of thiamethoxam by ensuring that the level of human exposure is well below the lowest dose at which these effects occurred in animal tests.

Residues in Water and Food

Dietary risks from food and water are not of concern.

Aggregate chronic dietary intake estimates (food plus drinking water) revealed that all population subgroups, including children 1–2 years old, the subpopulation that would ingest the most thiamethoxam relative to body weight, are expected to be exposed to less than 27% of the acceptable daily intake. Based on these estimates, the intermediate chronic dietary risk from thiamethoxam is not of health concern for all population subgroups.

Acute aggregate dietary intake estimates (food and water) revealed that all population subgroups, including children 1–2 years old, the subpopulation that would ingest the most thiamethoxam relative to body weight, are expected to be exposed to less than 11% of the acute reference dose, which is not a health concern.

The *Food and Drugs Act* prohibits the sale of adulterated food, that is, food containing a pesticide residue that exceeds the established maximum residue limit (MRL). Pesticide MRLs are established for the purposes of the *Food and Drugs Act* through the evaluation of scientific data under the *Pest Control Products Act*. Food containing a pesticide residue that does not exceed the established MRL does not pose an unacceptable health risk.

Residue trials conducted throughout Canada using end-use products containing thiamethoxam on pome fruits and potatoes were sufficient to propose MRLs for pome fruits and potatoes.

For the MRLs for this active ingredient, please refer to the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage in the Pesticides section of Canada.ca.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern provided that directions specified on the labels are observed.

Occupational Risks From Handling Thiamethoxam

Occupational risks are not of concern when thiamethoxam is used according to the proposed label directions, which include protective measures.

Farmers and pesticide applicators mixing, loading or applying either Actara 240SC Insecticide or Actara 25WG Insecticide as well as field workers re-entering treated fields can come in direct contact with thiamethoxam on the skin or through inhalation of spray mists. For this reason, the Actara 240SC Insecticide label specifies that anyone mixing or loading must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and boots and that anyone applying the product must wear coveralls and boots. In the case of Actara 25WG Insecticide, the label specifies that anyone mixing and loading must wear a long-sleeved shirt, long pants, chemical resistant gloves, socks and boots and that anyone applying must wear a long-sleeved shirt, long pants, socks and boots. Taking these label statements into consideration, precautionary measures, and the exposure duration, risks to farmers, applicators or postapplication workers are not a concern.

For bystanders, exposure is expected to be much less than that for workers and is considered

negligible. Therefore, health risks to bystanders are not of concern.

Environmental Considerations

What Happens When Thiamethoxam Is Introduced Into the Environment?

The risks to pollinators and aquatic invertebrates from outdoor uses of thiamethoxam have not been shown to be acceptable. As such, mitigation, including cancellation of some uses, has been proposed.

Thiamethoxam may enter the environment when applied by foliar spray or soil application to potatoes and pome fruit trees to control insect pests, as described in the original use pattern document ERC2007-01. Thiamethoxam can come in contact with soil when it is applied directly on the ground, or sprayed on foliage and it washes off onto the ground, or comes into contact with the ground when sprayed on crops. The length of time that thiamethoxam will persist in soil depends on various factors including soil type. In certain fields, thiamethoxam may persist long enough to carry over from one growing season to the next.

Major products formed from the microbial degradation of thiamethoxam in soil are CGA 322704 (clothianidin; also a registered pesticide) and CGA 355190, both of which can persist in soil.

Thiamethoxam may enter the aquatic environment through spray drift or run-off. In water, thiamethoxam is expected to dissipate relatively quickly if exposed to sunlight. In the absence of sunlight, thiamethoxam will be broken down more slowly by microbes. As such, thiamethoxam is moderately persistent in aquatic systems. CGA 322704 also dissipates relatively quickly if exposed to sunlight, but is moderately persistent in water in the absence of sunlight. Thiamethoxam and its soil transformation product CGA 322704 (clothianidin) can also leach through the soil into groundwater.

The toxicity of thiamethoxam and its major transformation products to terrestrial and aquatic organisms can be found in PRVD2017-24, ERC2007-01 and PSRD2018-02. Overall, there are risks to pollinators, other beneficial arthropods and aquatic invertebrates. As such, mitigation, including cancellation of some uses, has been proposed in PRVD2017-24 and PSRD2018-02.

Value Considerations

What Is the Value of Actara 25WG Insecticide and Actara 240SC Insecticide?

Actara 25WG Insecticide controls a variety of insect pests of potato, apple, crabapple, pear and oriental pear, Actara 240SC Insecticide controls insect pests of potato.

Actara 240SC Insecticide is an in-furrow treatment to control Colorado potato beetle, aphids and potato leafhopper on potato. Actara 25WG Insecticide is applied as a foliar spray and controls these same pests on potato, as well as plum curculio, mullein bug, spotted tentiform leafminer and rosy apple aphid on apple and crab apple, and plum curculio and pear psylla on pear and oriental pear. These insects are important pests of their respective crops. These products have acceptable value.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

Key Risk-Reduction Measures

Human Health

As workers could come into direct contact with thiamethoxam on the skin or through inhalation of spray mists, the Actara 240SC Insecticide label specifies that anyone mixing or loading must wear a long-sleeved shirt, long pants, chemical-resistant gloves, socks and boots and anyone applying the product must wear coveralls and boots. In the case of Actara 25WG Insecticide, the label specifies that anyone mixing and loading must wear a long-sleeved shirt, long pants, chemical resistant gloves, socks and boots and anyone applying the product must wear a long-sleeved shirt, long pants, socks and boots.

Environment

As a result of the pollinator re-evaluation of thiamethoxam and the special review on aquatic invertebrates, further risk mitigation measures for product labels are being proposed. See the documents below for more information.[12]

- Measures to Protect Pollinators, as found in PRVD2017-24, *Thiamethoxam and Its Associated End-Use Products: Pollinator Re-Evaluation.*
- Measures to Protect Aquatic Invertebrates, as found in PSRD2018-02, *Special Review of Thiamethoxam Risk to Aquatic Invertebrates: Proposed Decision for Consultation.*

The risk-reduction measures and other conditions of registration being proposed as a result of the re-evaluation review of the risk to pollinators and of the special review will apply to the end-use products listed in Table 1. Additionally, terrestrial buffer zones are required to protect non-target terrestrial plants.

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12 https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/public/consultations.html

Conclusion

The conditions of registration relating to the submission of additional information required under section 12 of the *Pest Control Products Act* for thiamethoxam and its associated end-use products as presented in Table1 have been met. To address potential risks to pollinators and aquatic invertebrates, amendments to the registrations of the end-use products have been proposed, including cancellation of some uses.

Health Canada's PMRA, under the authority of section 8 of the *Pest Control Products Act*, is proposing a three-year registration for the sale and use of Thiamethoxam Technical (Reg. No. 27445) and the end-use products listed in Table 1. The continued registration of USCs 5, 13, 14, and 27 of thiamethoxam are subject to the final outcome of the special review on aquatic invertebrates, and of the final decision on the pollinator re-evaluation.

Next Steps

Before making a final registration decision on Thiamethoxam, Actara 25WG Insecticide, Actara 240SC Insecticide, and other related end-use products, the PMRA will consider any comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 90 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision on Thiamethoxam, Actara 25WG Insecticide, Actara 240SC Insecticide, and other related end-use products, which will include its decision, the reasons for it, a summary of comments received on the proposed decision and Heath Canada's response to these comments.

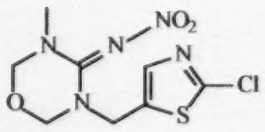
In addition, the confidential test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Thiamethoxam

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Thiamethoxam
Function	Insecticide
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	***(EZ)*-3-(2-chloro-1,3-thiazol-5-ylmethyl)-5-methyl-1,3,5-oxadiazinan-4-ylidene(nitro)amine**
2. Chemical Abstracts Service (CAS)	**3-[(2-chloro-5-thiazolyl)methyl]tetrahydro-5-methyl-*N*-nitro-4*H*-1,3,5-oxadiazin-4-imine**
CAS number	**153719-23-4**
Molecular formula	**$C_8H_{10}ClN_5O_3S$**
Molecular weight	**291.7**
Structural formula	
Purity of the active ingredient	**99.1 %**

1.2 Physical and Chemical Properties of the Active Ingredient and End-Use Product

Technical Product—Thiamethoxam Technical

Property	Result
Colour and physical state	Off white fine powder
Odour	Odourless
Melting range	139.1°C
Boiling point or range	Not applicable. The product is a solid
Density	1.57×10^3 kg/m^3
Vapour pressure at 20°C	2.7×10^{-9} Pa

Property	Result
Ultraviolet (UV)-visible spectrum	No significant absorption at wavelengths over 300 nm in neutral, acidic and basic solutions
Solubility in water at 20°C	4.1 g/L
Solubility in organic solvents at 20°C	Solvent — Solubility (g/100 mL) dichloromethane — 11 acetone — 4.8 methanol — 1.3 ethyl acetate — 0.7 toluene — 0.068 octanol — 0.062 hexane — < 0.0001
n-Octanol-water partition coefficient (K_{ow})	log K_{ow} = -0.13 ± 0.0017 at 25°C
Dissociation constant (pK_a)	No dissociation within the pH range 2 to 12
Stability (temperature, metal)	No thermal effect (peak) found between room temperature and the melting point of the substance. The technical grade active ingredient is not changed by contact with metals (stainless steel, cast steel, tin and aluminum) and with metal ions (Zn^{+2}, Al^{+3}, Cu^{+2} and Fe^{+2}).

End-Use Product—Actara 240SC Insecticide

Property	Result
Colour	Dark beige
Odour	Aromatic
Physical state	Liquid
Formulation type	Suspension (SU)
Label concentration	240 g/L
Container material and description	High density polyethylene (HDPE)
Density	1.113 g/mL at 20°C
pH of 1% dispersion in water	5.6 (1% aqueous)
Oxidizing or reducing action	The product has no oxidizing or reducing properties.
Storage stability	The product was found to be stable after storage for at least three years at ambient temperature.
Corrosion characteristics	A physical evaluation of the test system indicated no physical changes in the test substance or containers.
Explodability	The product does not have explosive properties.

End-Use Product—Actara 25WG Insecticide

Property	Result
Colour	Light brown
Odour	Musty
Physical state	Solid
Formulation type	Wettable granules
Label concentration	25%
Container material and description	High density polyethylene (HDPE)
Density	0.47 g/mL at 20°C
pH of 1% dispersion in water	7–11 (1% aqueous solution at 25°C)
Oxidizing or reducing action	The product has no oxidizing or reducing properties.
Storage stability	The product was found to be stable after storage for at least three years at ambient temperature.
Corrosion characteristics	No physical changes are observed in the test container (HDPE) after storage for at least three months.
Explodability	Test results show the product not to be explosive

1.3 Directions for Use

Actara 25WG Insecticide

Actara 25WG Insecticide is applied as a foliar spray. On potato, it controls Colorado potato beetle, aphids and potato leafhopper with up to two applications per year at 105 g product/ha with a 7–10 day reapplication interval. On apple and crab apple, it controls plum curulio and mullein bug at 315–385 g product/ha, spotted teniform leafminer at 315 g product/ha, and rosy apple aphid at 160 g product/ha, with up to three applications per year. On pear and oriental pear it controls plum curulio and pear psylla at 315–385 g product/ha with up to two applications per year.

Actara 240SC Insecticide

Actara 240SC Insecticide is applied in-furrow to potato at 3.4–4.4 mL product/100 m to control Colorado potato beetle, aphids and potato leafhopper.

1.4 Mode of Action

Thiamethoxam is a neonicotinoid insecticide in the Insecticide Resistance Action Committee's Mode of Action Group 4A. It affects insect nerves and acts as a nicotinic acetylcholine receptor agonist. Thiamethoxam is most active through ingestion. It is mobile in the xylem of plants, showing systemic activity by root uptake but is only translaminar active by foliar application.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods provided for the analysis of the active ingredient and impurities in the technical product have been validated and assessed to be acceptable for the determinations.

2.2 Method for Formulation Analysis

The method provided for the analysis of the active ingredient in the formulation has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.3 Methods for Residue Analysis

High performance liquid chromatography methods with ultra-violet or mass spectrometric detection (HPLC-UV or MS; Method AG-675 for plant and animal matrices) were developed for data gathering and enforcement purposes. These methods fulfilled the requirements with regards to specificity, accuracy and precision at the respective method limit of quantitation. Acceptable recoveries (70–120%) were obtained in plant and animal matrices. The proposed enforcement methods were successfully validated in plant and animal matrices by an independent laboratory. Adequate extraction efficiencies were demonstrated using radiolabelled plant and animal matrices.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

Thiamethoxam is a broad spectrum nitroguanidine insecticide which belongs to the neonicotinoid pesticidal class. It exerts its pesticidal mode of action by interfering with the nicotinic acetylcholine receptors of the insect's nervous system. Thiamethoxam has a lower affinity for vertebrate nicotinic receptors than those of insects. A detailed review of the toxicology database for thiamethoxam was conducted. The database is complete, consisting of the full array of toxicity studies currently required for hazard assessment purposes. In addition, a suite of special studies were conducted to investigate the etiology of liver tumours in the mouse oncogenicity study. The studies in the database were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. The scientific quality of the data is high and the database is considered adequate to characterize the potential health hazards associated with thiamethoxam.

Toxicokinetic investigations were conducted in rats and mice with thiamethoxam, radiolabelled with ^{14}C in either the oxadiazine or thiazole ring, administered primarily via the diet or gavage at various dose levels for different durations. These investigations also included comparative metabolism studies in rats and mice which examined blood metabolite profiles in both species following extended dietary dosing.

Absorption, distribution, metabolism and excretion of thiamethoxam were independent of sex, dose level, pre-treatment and radiolabel position. In both rats and mice, thiamethoxam was

rapidly absorbed and eliminated. Blood concentrations of radioactivity peaked between one and six hours post-dosing in rats and at 0.5 hours in mice. The half-lives of elimination of radioactivity in blood were three and four hours for rats and mice, respectively. In mice, approximately 72% of the administered dose (AD) was excreted in the urine and 19% was excreted in the feces. In rats, > 84% of the AD was excreted in the urine and ≤ 6% was excreted in the feces. Elimination via expired air was negligible in both species.

Radioactivity was widely distributed to tissues, with the highest concentrations in rats detected in skeletal muscle within eight hours of dosing. Tissue residues in rats seven days post-dosing were very low (less than 1% of the AD), with the highest amounts detected in liver. In mice, the highest tissue residues at 72 hours post-dosing were found in liver, with total body radioactivity less than 1% of the AD.

The major pathways of thiamethoxam metabolism in rats and mice involve either oxidative loss of the oxadiazine ring to form CGA322704 (also known as clothianidin), or alternatively, oxidative N-demethylation to form CGA330050. Further metabolism of both of these metabolites results in the formation of the other major metabolite, CGA265307. Unchanged thiamethoxam was the major component in blood extracts (78% mice, 82% rats). In mice, CGA322704, CGA265307 and CGA330050 were detected in blood at comparable levels (10–15%). In rats, CGA322704 was detected in blood (16%) with only trace amounts of CGA265307 (0.3%). CGA330050 was not detected in blood in rats. Only three urinary metabolites accounted for greater than 1% of the AD in rats. Unchanged thiamethoxam accounted for 69–83% of the AD in rats (31–44% in mice); CGA322704 was the major urinary metabolite in rats (5–13% of the AD) and mice (8–12%). CGA265307 accounted for ≤ 2% of the AD in rats and 9–18% of the AD in mice. The identification of the major metabolites in rats and mice is presented in Appendix I, Table 2.

Concentrations of the metabolite CGA265307 were approximately 22-fold greater in mouse plasma than in rat plasma after one week of dietary administration of thiamethoxam. After ten weeks of dietary administration, the concentration of CGA265307 in mouse plasma had increased approximately 3.6-fold compared to that recorded after one week of dietary administration, suggesting induction of metabolic pathways, whereas that in rat plasma had lessened with extended administration. As a result, plasma concentrations of CGA265307 were up to 140-fold greater in mice than rats. The difference between the plasma levels of CGA330050 in rats and mice was up to 15-fold over the 10-week dosing duration with higher amounts in mouse plasma. The major difference between metabolism in rats and mice may contribute to differences in long-term toxicity.

In vitro investigations with liver fractions obtained from rat, mouse and human tissue preparations revealed that, depending on the metabolism pathway involved (either via oxidative loss of the oxadiazine ring to form CGA322704 or via oxidative N-demethylation to form CGA330050), metabolic rates in mouse liver were 54-fold (via CGA322704) and 87-fold (via CGA330050) higher than those in rat liver and 371-fold and 238-fold higher, respectively, than those in human liver.

In acute toxicity studies, technical thiamethoxam was slightly toxic to rats and moderately toxic to mice via the oral route and of low toxicity to rats via the dermal and inhalation routes of exposure. Thiamethoxam was minimally irritating to rabbit eyes and non-irritating to rabbit skin. It was non-sensitizing in a maximization test in guinea pigs. The metabolite CGA322704 was of low acute toxicity in rats via the oral route of administration.

Actara 240SC Insecticide was of low toxicity via the oral route in rats, and via the dermal route in rabbits. It was slightly acutely toxicity via the inhalation route in rats. Actara 240SC Insecticide was non-irritating to the eyes of rabbits and slightly irritating to rabbit skin. It was not a dermal sensitizer in guinea pigs via the Buehler method.

Actara 25WG Insecticide was of low toxicity via the oral and inhalation routes of exposure in rats, and of low toxicity via the dermal route in rabbits. It was mildly irritating to the eyes and slightly irritating to the skin of rabbits. Actara 25WG Insecticide was not a dermal sensitizer in guinea pigs using the Buehler method.

In the guideline repeat-dose dietary toxicity studies of short-term to long-term duration, the primary target organs of toxicity for thiamethoxam were the kidney (rats), liver (rats, mice, dogs), and testes (dogs). Male rats were more sensitive than female rats to the effects of thiamethoxam on the kidneys. Effects in this organ included hyaline change of renal tubular epithelium, basophilic proliferation of renal tubules, dilatation of renal pelvis and increased organ weight. The observed hyaline change in the proximal convoluted tubules of the male rat kidneys was attributed to the accumulation of alpha 2u-globulin, a protein that is unique to male rats. The results of immunohistochemical assessment of renal tissue in rats following short-term to long-term dietary dosing revealed increased accumulation of renal alpha 2u-globulin in male rats receiving thiamethoxam. Similar findings were not observed in thiamethoxam-treated females or control animals of either sex. It should be noted, however, that hyaline change, consisting of eosinophilic droplets within the cytoplasm of the proximal convoluted tubules, was observed in one high-dose F_1 generation female in one of the two-generation dietary rat reproductive toxicity studies. In addition, other kidney toxicity was observed in female rats in the repeat-dose dietary studies, including chronic tubular lesions and nephrocalcinosis.

Liver toxicity, in the form of hepatocellular hypertrophy, increased liver weights and associated changes in clinical biochemical parameters, was also observed in rats but these alterations were noted at higher dose levels than those producing kidney toxicity. In mice, liver pathology included hepatocellular hypertrophy, necrosis of single hepatocytes, lymphocytic infiltration and Kupffer cell pigmentation, and hyperplasia. Male mice were slightly more sensitive than females to liver toxicity. In dogs, accumulation of pigment within hepatic Kupffer cells, as well as changes in liver clinical biochemical parameters were noted.

In dogs, testicular effects were a noteworthy finding following repeated dietary dosing. In the 90-day toxicity study, severely decreased food consumption and concomitant body weight loss at the highest dose level necessitated cessation of treatment for seven days and resumption of dosing with a lower dose level. Animals from this group had decreased testis weights, reduced spermatogenesis and minimal to moderate occurrence of spermatic giant cells in the testes.

Atrophy of the seminiferous tubules was observed in one high-dose male. Atrophy of the seminiferous tubules and decreased testes weight were also observed at a lower dose level in male dogs after exposure to thiamethoxam for 12 months.

In addition to the effects on kidneys, liver and testes noted above, changes in other organs were observed at the higher dose levels following repeated dietary dosing. These included decreased ovarian weights and ovarian atrophy in mice in the 90-day toxicity study and decreased ovary weights associated with delayed maturation of the ovaries in dogs in the 90-day toxicity study. Increased adrenal and thyroid weights were also observed at the higher dose levels in the repeat-dose rat studies.

A rat repeat-dose dermal toxicity study identified systemic toxicity (liver, kidney effects) that was consistent with that observed in rat oral toxicity studies. At the highest dose level, there was evidence of chronic tubular lesions in kidneys in females, whereas in males, the kidney findings consisted of renal tubule hyaline change. At the next lower dose level, liver toxicity was observed in females only. These results demonstrated that females were more sensitive than males following dermal dosing.

There was no evidence of genotoxicity in a battery of in vitro and in vivo genotoxicity studies conducted with thiamethoxam. There was no evidence of oncogenicity after long-term repeated dietary dosing in rats. However, body weight was unaffected in thiamethoxam-treated males in the long-term rat study, suggesting that animals could have tolerated higher dose levels. Despite this, there was evidence of systemic toxicity in males which included chronic nephropathy and lymphocytic infiltration in the kidneys. Decreased body weight gain, chronic tubular lesions in the kidneys and foci of cellular alteration in the liver were observed in females at a higher dose level.

In mice, long-term dietary dosing resulted in an increased incidence of benign and malignant liver tumours in both males and females. The incidence of hepatocellular adenomas was increased ($p<0.01$ pair-wise) in both sexes at the two highest dose levels. An increase ($p<0.05$) was also observed in females at the next lower dose level. At this same dose level, the incidence of adenomas in males was higher than concurrent controls; however, it was not statistically significantly different from that of the concurrent controls and it fell within the range of the historical control data. With regards to hepatocellular carcinomas, the incidence was increased ($p<0.01$) in both sexes at the highest dose level. At the next lower dose level, the incidence of carcinomas was increased ($p<0.05$) in males but fell within the range of the historical controls whereas the incidence in females at this dose level, although not statistically significantly different from that of the concurrent control, fell outside the upper range of the historical control data. The combined incidences of hepatocellular adenomas and carcinomas in both sexes was significantly ($p<0.01$) elevated at the two highest dose levels. Historical control data for combined incidences were not available. At the next lower dose level, the combined incidence in females was significantly ($p<0.05$) increased; the incidence in males at this dose level was slightly higher than concurrent controls, but it was not statistically significant. In females, the increase was largely driven by the adenomas since no carcinomas were observed at this dose level.

Treatment with thiamethoxam resulted in an increase in the number of animals with multiple liver tumours; however, the tumours did not have an impact on group survival. The results of this study indicated that thiamethoxam produced liver tumours only at dose levels producing overt indications of liver toxicity.

Thiamethoxam was proposed to produce liver tumours in mice as a result of cytotoxicity and cell death, followed by increased cell replication rates, and ultimately, the production of tumours. A series of special studies were conducted to investigate the etiology of the mouse liver tumours. The special studies included investigation of differential metabolism in mice and rats, as well as in vitro comparison of thiamethoxam metabolism by microsomal preparations from mouse, rat and human liver (discussed previously). The studies also addressed histological and biochemical changes in mice and rats. The investigative studies included dietary administration to rats and mice for various study durations of up to 50 weeks, employing dose levels consistent with mouse tumorigenic dose levels. In mice, decreased cholesterol was identified as an early indicator of liver perturbation, occurring as early as seven days, on the basis of these dietary studies. In light of this finding, a comparative hepatotoxicity study in weanling and adult mice following seven days of dietary exposure was also provided, which investigated the sensitivity of weanling and adult mice to the cholesterol-lowering effects of thiamethoxam. The comparative hepatotoxicity of the major metabolites, CGA322704, CGA265307, and CGA330050, with thiamethoxam was also investigated in dietary feeding studies in rats and mice.

The findings in this suite of special studies showed a clear effect of both dose and duration of treatment on hepatic changes in mice, supporting a sequence of events, from disturbance of cellular homeostasis to hepatotoxicity, hepatocellular lethality, and compensatory cell proliferation. Effects in mice noted early on in treatment included reduced cholesterol and serum protein (after one week of dietary dosing) and increased alanine aminotransferase (after ten weeks of dietary dosing). Hepatocellular hypertrophy, necrosis, and apoptosis were noted later in mice, from week 10 onwards, whereas inflammatory cell infiltration and increased aspartate aminotransferase were noted at week 20. Increased mitotic index was observed in mice after 40 weeks of dosing. At higher dose levels in mice, increases in the mean hepatic concentration of reduced and oxidized glutathione were observed. Treatment with thiamethoxam in mice caused an increase in hepatic γ-glutamylcysteine synthetase and hepatic glutathione S-transferase activity. Thus, thiamethoxam can be considered a moderate inducer of liver phase II xenobiotic metabolizing enzymes in mice. Liver effects were noted in two mouse strains (Tif:MAGf and CD-1), suggesting that the toxicity noted was not strain-specific. The temporal and dose relationship for liver toxicity in mice was not observed in rats; similar testing did not identify adverse effects on biochemistry and histopathology parameters, nor was there an increase in enzyme induction or cell replication rates. These differences in liver toxicity between rats and mice suggested a differential metabolism of thiamethoxam in these species.

This differential metabolism between rats and mice was confirmed in previously-mentioned studies that demonstrated a species difference in production of metabolites CGA265307 and CGA330050; over time, mice showed induction of metabolism with high levels of CGA265307 and CGA330050, whereas rats showed a reduction in metabolism.

The in vitro data demonstrated a similar difference, as rate conversions in mouse liver were much higher than those in rat liver fractions. The rate conversions in human liver were even lower than in rat liver, suggesting that metabolism of thiamethoxam to the major metabolites would be much lower in humans.

The metabolites CGA322704 and CGA265307 did not produce evidence of hepatotoxicity in mice or rats. CGA330050 produced a spectrum of hepatotoxicity similar to thiamethoxam following repeated dietary dosing in mice, with evidence of decreased cholesterol and serum protein, increased hepatocellular hypertrophy, necrosis, apoptosis, and inflammatory cell infiltration. Hepatic effects in rats fed the metabolite CGA330050 were limited to increased liver enzymes, suggesting a lack of liver toxicity in rats. These findings, combined with the evidence of differential metabolism summarized above, suggest that the metabolite CGS330050 is a major contributor to the thiamethoxam-induced hepatotoxicity observed in mice. Another possible contributor to the development of hepatotoxicity in thiamethoxam-treated mice is CGA265307. Although this metabolite was not hepatotoxic in rats or mice, it did inhibit inducible nitric oxide synthase. Nitric oxide produced by these enzymes is known to have a regulatory role in the liver in modulating the adverse effects of Tumour Necrosis Factor alpha (TNFα) released from endothelial cells during chemically induced hepatotoxicity. Thus, inhibition of these enzymes may have exacerbated the liver toxicity resulting from the hepatotoxic metabolite, CGA330050. Results of the comparative study in weanling and adult mice indicated that plasma levels of thiamethoxam and metabolites CGA322704, CGA265307, and CGA330050 were up to twofold higher in weanlings than in adults. The pattern of metabolism and ratio of metabolites to each other and to thiamethoxam was the same in both age groups. Despite the higher plasma levels in weanling mice compared to adult mice, the reductions in plasma cholesterol and the changes in liver morphology (increased centrilobular vacuolation and decreased eosinophilia) in weanlings were significantly less than in adults. Weanlings were at least twofold less susceptible to cholesterol reduction than adults across the dose levels tested.

Based on the overall evidence, the increase in mouse liver tumour response appears to be linked to the greater ability of the mouse, compared to humans and rats, to metabolize thiamethoxam to a hepatotoxic metabolite. As a result, it was determined that a threshold approach to the cancer risk assessment could be taken.

There was no evidence of sensitivity of the young in gavage developmental toxicity studies in rats and rabbits conducted with thiamethoxam. In rats, reduced fetal body weights and an increase in skeletal variations (asymmetrically shaped 6th sternebrae and irregular ossification of occipital bone) were observed at a dose level that produced reductions in body weight as well as clinical signs of toxicity in dams. In the rabbit study, the findings were similar in that there was a reduction in fetal body weight and a slightly increased incidence of fetal skeletal findings (fused or asymmetrically shaped sternebrae). The skeletal findings in rabbits were increased on a fetal basis only, and the incidences were only slightly outside the upper end of the historical control values. Maternal toxicity was also observed at the same dose level, consisting of reduced body weight and food consumption, uterine hemorrhage, post-implantation loss, and death in the dams.

Two two-generation reproductive toxicity studies in which rats were administered thiamethoxam in the diet were available. There were no effects on mating, gestation or fertility in either study. In the first study, which included two litters per generation, kidney toxicity was observed in the parental males, consistent with the findings in the short-term studies. Kidney hyaline change was observed in one high-dose parental F_1 female which, as mentioned previously, raised some uncertainty regarding the claim that the finding in male rats in numerous other studies in the database was due to alpha 2u-globulin accumulation in the proximal convoluted tubules. In offspring, decreases in body weight and bodyweight gains were observed in the postnatal period at dose levels that were toxic to parental males. With respect to reproductive toxicity, an increase in both the incidence and severity of atrophy of the seminiferous tubules was observed in the F_1 generation in the absence of parental systemic toxicity, suggesting potential sensitivity of the young. This atrophy was not observed in the F_0 generation, nor was it observed in any of the short-term or chronic toxicity studies. In this reproductive toxicity study, there was reduced sperm motility at all dose levels in both generations; however, the findings were equivocal as there was no clear dose-response, the data were highly variable, and there was no effect on sperm count or morphology. A separate, complementary study was conducted to investigate these findings. Although the results indicated that technical error was the likely cause of the reduced sperm motility in the two-generation study, this complementary study was limited to analysis of F_0 animals and thus, no information relevant to the sperm motility finding in F_1 animals was available. For this reason, no definitive conclusion can be made regarding a possible association between the sperm observations and seminiferous tubule atrophy observed in the F_1 animals in this study. It bears noting that atrophy of the seminiferous tubules was observed in adult dogs in both the 90-day and the 12-month toxicity studies.

A second two-generation reproductive toxicity study with similar dose levels as the first study was conducted. Effects in parental animals included reductions in body weight, renal pathology (males), and changes in the weights of various organs, including increased kidney (males) and decreased pituitary (females) weights. Offspring toxicity was observed at a higher dose level and consisted of pup deaths occurring during postnatal weeks 3-4 as well as decreases in litter weights and a slight delay in preputial separation. With respect to reproductive toxicity, testicular effects were again a prominent finding with minimal germ cell loss or disorganization and Sertoli cell vacuolation (F_1) occurring at the highest dose level. With regards to effects on sperm motility, reductions were observed (F_0 and F_1) but only at the highest dose level. At the next lower dose level, which was also toxic to parental animals (kidney effects in males, reduced pituitary weights in females), reduced testes weights (F_1) were observed. Decreased sperm counts occurred in F_1 males at a dose level that was not toxic to parental animals; since these effects were observed only after in utero and postnatal exposure, this study provides evidence of sensitivity of the young.

In an acute neurotoxicity study, rats exposed via gavage to thiamethoxam demonstrated alterations in the functional observation battery and in locomotor activity parameters. These alterations included drooped palpebral closure, increased forelimb grip strength and decreased locomotor activity. A higher dose produced more pronounced signs of toxicity, including death, abnormal body tone, ptosis, impaired respiration, tremors, crouched-over posture, impaired gait, and uncoordinated landing in the righting reflex test. In a repeat-dose dietary neurotoxicity study in rats, there was no evidence of neurotoxicity. There was no neurohistopathology observed in

either the acute or repeat-dose neurotoxicity study. A dietary developmental neurotoxicity (DNT) study in rats was available. In this study, treatment-related findings were observed at the highest dose level only. In maternal animals, reductions in food consumption as well as slight reduction in body weight and weight gain occurred during the gestation and lactation periods. Offspring toxicity at the highest dose level consisted of reduced body weights throughout the pre-weaning and post-weaning periods as well as delayed sexual maturation in males. High variability in the female sexual maturation data precluded a determination of treatment-related changes. High-dose offspring had reduced brain weights (males, postnatal day [PND] 12 and 63; females, PND 12). Changes in brain morphometric measurements were also observed in high-dose animals at PND 12 and at study termination. At PND 12, males had reductions in the molecular layer of the cerebellum and the cerebellum length while females had reduced thalamus width. At PND 63, treatment with thiamethoxam was associated with reduced dorsal cortex thickness as well as decreases in thalamus, hippocampus, and overall thalamus/cortex widths in both sexes. In addition, there was a reduction in thickness of the piriform cortex and corpus callosum and in the thalamus height in males. There was no effect on startle response or on acquisition of learning or memory during performance of the Y water maze. It was noted, however, that the maze design lacked complexity and as such the results of the water maze were of limited utility. The results of this study indicated serious effects in offspring in the presence of slight toxicity in maternal animals.

The identification of the major metabolites in rats and mice is reported in Appendix I, Table 2. The results of the toxicology studies conducted on laboratory animals with thiamethoxam and its metabolites, and the associated end-use products Actara 240SC and Actara 25WG are reported in Appendix I, Table 3 and Table 4 respectively.. The toxicology reference values for human health risk assessment are summarized in Appendix I, Table 5.

Incident Reports

As of 31 January 2018, there were 32 human incidents and 39 domestic animal incidents reporting the active ingredient thiamethoxam, alone or in combination with other active ingredients.

Human incidents were minor or moderate in nature. In the majority of Canadian incidents, thiamethoxam was a component of a seed treatment product that contained multiple active ingredients. In four cases, individuals reported exposure to a product used as a spray. In more than half of the cases, the route of exposure was skin and/or respiratory (some individuals reported both routes of exposure). Dermal exposures resulted in signs like pruritus, erythema, rash, and paresthesia. Those exposed via the respiratory route reported chest discomfort, malaise, dizziness, and headache. In moderate cases, tremors, difficulty breathing, and more serious skin lesions were reported.

Domestic animal incidents were classified as minor, moderate, major, or death. The majority of cases were related to ingestion of seed treated with thiamethoxam, alone or in combination with other active ingredients. Half of the cases involved livestock and the predominant effects were nervous and muscular signs (ataxia, gait disturbance, and tremor). The remaining cases involved

cats and dogs and most signs were gastrointestinal in nature (anorexia, vomiting, diarrhea, and weight decrease).

These incident reports were considered in this evaluation and did not affect the risk assessment.

This exposure scenario is not anticipated with the proposed products because most incidents involved the exposure to small grains treated with thiamethoxam and other active ingredients.

***Pest Control Products Act* Hazard Characterization**

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, extensive data were available for thiamethoxam. The database contains the full complement of required studies including gavage developmental toxicity studies in rats and rabbits, two dietary two-generation reproductive toxicity studies in rats, and a dietary DNT study in rats. In addition, a supplemental comparative hepatotoxicity study in weanling and adult mice following seven days of dietary exposure was provided, which investigated the sensitivity of weanling and adult mice to the cholesterol-lowering effects of thiamethoxam.

With respect to sensitivity of the young animal to liver toxicity, weanling mice were at least twofold less sensitive than adults to reductions in plasma cholesterol, and also displayed less severe liver pathology compared to adult mice despite having higher plasma levels of thiamethoxam and its major metabolites compared to adults.

In developmental toxicity studies in rats and rabbits, reduced fetal weights and skeletal findings were observed in the presence of maternal toxicity. In rabbits, post-implantation losses were noted in the presence of severe maternal toxicity. In the DNT study, reduced brain weights and alterations in brain morphometric parameters were noted at the high-dose level in both male and female offspring in the presence of slight maternal toxicity (minimal body weight effects). Reduced pup body weight and delayed sexual maturation in males were also noted at this dose level.

Thiamethoxam did not affect mating, gestation, or fertility in either reproductive toxicity study or in the DNT study. However, there was evidence in both reproductive toxicity studies that the young may be more sensitive to thiamethoxam toxicity following in utero and postnatal exposure. In the first study, atrophy of the seminiferous tubules was observed in the F_1 generation in the absence of parental systemic toxicity. A reduction in sperm motility in both generations was considered equivocal due to issues that included highly variable data and lack of effect on sperm count or morphology. Additional investigation of this finding was limited in that only F_0 animals were examined; thus no information was available on animals that received in utero and postnatal exposure. This lesion was not observed in the F_0 generation, nor was it observed in any of the repeat-dose, including chronic toxicity, studies in rodents. For this reason,

no definitive conclusion can be made regarding a possible association between this observation and seminiferous tubule atrophy observed in the F_1 animals. Atrophy of the seminiferous tubules and reduced testicular weights were observed in adult dogs in both the 90-day and the 12-month toxicity studies. In the second reproductive toxicity study, with similar dose levels as the first study, offspring toxicity (decreased litter weights, slightly delayed preputial separation, and pup deaths during postnatal weeks 3–4) occurred at the highest dose level which was also toxic to parental animals. Minimal germ cell loss or disorganization and Sertoli cell vacuolation (F_1), as well as reduced sperm motility (F_0 and F_1) also occurred at this dose level. Decreased sperm counts in F_1 males occurred at a lower dose level in the absence of parental systemic toxicity indicating that the young may be more sensitive to thiamethoxam toxicity following in utero and postnatal exposure.

Overall, the toxicology database of thiamethoxam is considered complete and all required studies for assessing risk to infants and children were available. The effects on offspring brain weight and morphology in the DNT study were considered serious although the level of concern was tempered by the presence of maternal toxicity. Concern regarding the effects on offspring testes (seminiferous tubule atrophy, reduced sperm counts) observed in the absence of maternal toxicity in the reproductive toxicity studies was partially tempered by the absence of effect on reproductive indices, recognizing that these indices may be an insensitive measure in rodents in view of their fecundity. Based on the available information, the *Pest Control Products Act* factor was reduced to threefold.

3.2 Determination of Acute Reference Dose

General Population (including females 13 to 49 years of age, infants and children)

To estimate acute dietary risk, the DNT study with a NOAEL of 35 mg/kg bw/day was selected for risk assessment. At the LOAEL of 298 mg/kg bw/day, reduced pup weights, delayed sexual maturation, reduced brain weights and altered brain morphometrics were observed. The brain effects potentially could result from a single exposure and therefore these findings are relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to threefold. Accordingly, the composite assessment factor (CAF) is 300.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{35 \text{ mg/kg bw/day}}{300} = 0.1 \text{ mg/kg bw}$$

3.3 Determination of Acceptable Daily Intake

Acceptable Daily Intake (ADI)

General Population (including females 13 to 49 years of age, infants and children)

To estimate dietary risk following repeated exposure, the combined results of the two reproductive toxicity studies were selected for risk assessment. The highest NOAEL of 1.2 mg/kg bw/day was established based on testicular and sperm effects in F_1 animals occurring at the study LOAELs of 1.8 and 3.0 mg/kg bw/day. These studies provided the lowest NOAEL in the database. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to threefold. The resulting CAF is thus 300.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{1.2 \text{ mg/kg bw/day}}{300} = 0.004 \text{ mg/kg bw/day}$$

Cancer Assessment

Results of in vitro and in vivo genotoxicity studies indicated that thiamethoxam was not genotoxic. As well, thiamethoxam was not oncogenic in rats. However, a treatment-related increased incidence of liver tumours was observed in mice. The increase in tumour response was linked to the greater ability of the mouse, compared to humans and rats, to metabolize thiamethoxam to a hepatotoxic metabolite. Although the pattern of tumour formation (enzyme changes, hypertrophy, apoptosis, necrosis and cell turn-over) is biologically plausible in humans, a prolonged exposure to high concentrations of thiamethoxam would be required to elicit this effect. As a result, it was determined that a threshold approach to the cancer risk assessment could be taken. The ADI provides a margin of 925 to the NOAEL of 3.7 mg/kg bw/day for liver tumours in female mice and is considered protective of all populations.

Cumulative Assessment

The *Pest Control Products Act* requires the PMRA to consider the cumulative effects of pest control products that have a common mechanism of toxicity. Thiamethoxam belongs to a group of insecticides commonly known as the neonicotinoids. Upon completion of the re-evaluation of thiamethoxam, it will be determined whether a cumulative effects assessment is necessary and if so, this will be performed with all relevant chemicals of the common mechanism group.

3.4 Occupational and Residential Risk Assessment

3.4.1 Toxicological Endpoints

Occupational exposure to thiamethoxam is characterized as short- to intermediate-term in duration and is predominantly by the dermal and inhalation routes for mixers, loaders, and

applicators. For postapplication re-entry workers, the exposure is characterized as short- to intermediate-term and predominantly by the dermal route.

Short-, Intermediate- and Long-term Inhalation

Repeat-dose inhalation toxicity studies were not available. For exposures of all durations via the inhalation route, the NOAEL of 1.2 mg/kg bw/day from the combined results of the two reproductive toxicity studies was selected for risk assessment. The combined results of these studies revealed testicular and sperm toxicity in the F_1 generation. These effects were only observed after in utero and postnatal exposure. Worker populations could include pregnant or lactating women and therefore these endpoints were considered appropriate for the occupational risk assessment. The target Margin of Exposure (MOE) is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of threefold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of the NOAEL from the reproductive toxicity studies and MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

Short-, Intermediate- and Long-term Dermal

For occupational exposures of all durations via the dermal route, the NOAEL of 1.2 mg/kg bw/day from combined results of the two reproductive toxicity studies was selected for risk assessment. The combined results of these studies identified testicular and sperm toxicity in the F_1 generation. These effects were only observed after in utero and postnatal exposure. Worker populations could include pregnant or lactating women and therefore these endpoints were considered appropriate for the occupational risk assessment. The available 28-day dermal toxicity study did not assess the relevant endpoints of concern, namely, reproductive organ toxicity in pups following prenatal or postnatal exposure. The target MOE is 300, which includes uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability as well as a factor of threefold for the reasons outlined in the *Pest Control Products Act* Hazard Characterization section. The selection of the NOAEL from the reproductive toxicity studies and MOE is considered protective of all populations, including nursing infants and the unborn children of exposed female workers.

3.4.1.1 Dermal Absorption

Based on in vivo rodent dermal absorption studies conducted using various formulations of thiamethoxam, as summarized in Evaluation Report ERC2007-01, *Thiamethoxam*, the dermal absorption value for thiamethoxam was calculated to be 2.5%.

3.4.2 Occupational Exposure and Risk

3.4.2.1 Mixer/loader/applicator Exposure and Risk Assessment

Dermal and inhalation exposure estimates were derived for mixers/loaders/applicators applying thiamethoxam either in-furrow to potatoes (Actara 240SC Insecticide) or through foliar application to potatoes and pome fruits (Actara 25WG Insecticide). Only ground application was

considered (groundboom, in-furrow, and airblast). Exposure estimates were based on the Pesticide Handler Exposure Database (PHED) Version 1.1 as well as mixers/loaders wearing a single layer of clothing (long pants and long sleeved shirt) plus gloves and applicators wearing a single layer and no gloves (Actara 25WG Insecticide) or coveralls over a single layer of clothing and no gloves (Actara 240SC Insecticide).

Dermal exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 2.5% dermal absorption. Inhalation exposure was estimated by coupling the unit exposure values with the amount of product handled per day with 100% inhalation absorption. Exposure was normalized to mg/kg bw/day by using a 70 kg adult body weight.

Exposure estimates were compared to the toxicological endpoints (no observed adverse effects levels (NOAELs)) to obtain the margin of exposure (MOE); the target MOE is 300.

Dermal and inhalation risks to workers, mixing, loading and applying thiamethoxam were not of concern (MOEs were above the target MOE; Appendix I, Table 6).

The endpoints selected for worker risk assessment are also protective of any potential cancer findings and there are no health risks of concern.

3.4.2.2 Exposure and Risk Assessment for Workers Entering Treated Areas

Post-application exposure to Actara 240SC Insecticide is expected to be minimal since it is applied in-furrow and residues on potato foliage are not expected to occur.

However, there is potential for exposure to workers re-entering areas treated with Actara 25WG Insecticide to perform a variety of tasks such as pruning, scouting, handline irrigating, hand harvesting and thinning.

Inhalation risks to post-application workers were deemed negligible considering the vapour pressure of thiamethoxam and the 12-hour restricted-entry interval (REI). Therefore, the postapplication risk assessment for Actara 25WG Insecticide is limited to dermal exposure.

Dermal exposure to workers re-entering treated areas is calculated by coupling crop-specific dislodgeable foliar residue (DFR) values with activity-specific transfer coefficients (TCs). Activity-specific transfer coefficients are based on Agricultural Re-entry Task Force (ARTF) data, of which Syngenta is a member. An 8 hour work day and a 70 kg body weight are assumed.

Based on a dislodgeable foliar residue (DFR) study conducted on apples in Oregon, Washington and New York, and summarized in Evaluation Report ERC2007-01, *Thiamethoxam*, the peak DFR value of 0.83 $\mu g/cm^2$ from the New York site was used to estimate exposure associated with postapplication activities.

Exposure estimates were coupled with the NOAEL of 1.2 mg/kg bw/day from the rat reproduction study. MOEs for all post-application activities for pome fruit production exceed the target MOE of 300. Therefore, dermal risks to workers re-entering treated orchards to perform post-application activities were not of concern (See Appendix I, Table 7). Re-entry activities

associated with potato cultivation are generally less intensive than pome fruit cultivation and are therefore also considered acceptable.

The endpoints selected for worker risk assessment are also protective of any potential cancer findings and there are no health risks of concern.

Thiamethoxam can metabolise to clothianidin in plants. Workers entering treated fields and orchards may potentially be exposed to clothianidin. This scenario was evaluated and it was determined, based on the metabolic pathway of thiamethoxam in plants and the toxicology profiles of thiamethoxam and clothianidin, that the current risk assessment is adequately protective.

3.4.2.3 Bystander Exposure and Risk

Bystander exposure should be negligible since the potential for drift is expected to be minimal. Appropriate label statements are included on both the Actara 240SC Insecticide and Actara 25WG Insecticide labels to ensure that the products will only be applied when there is low risk of drift when taking into consideration wind speed, wind direction, temperature inversions, application equipment and sprayer settings.

3.4.3 Residential Exposure and Risk Assessment

Actara 240SC Insecticide and Actara 25WG Insecticide are commercial marketing-class products for use in commercial settings. Therefore, residential handler and postapplication exposure assessments are not required.

3.5 Food Residues Exposure Assessment

3.5.1 Residues in Plant and Animal Foodstuffs

The residue definition for risk assessment and enforcement in plant products and animal commodities is thiamethoxam and the metabolite CGA 322704. The data gathering/enforcement analytical methods are valid for the quantitation of residues of thiamethoxam and CGA 322704 in crop and livestock matrices. The available storage stability data are adequate to support the storage intervals and conditions of samples from all supervised field trials. Supervised crop field trials conducted throughout Canada using end-use products containing thiamethoxam at approved rates in or on pome fruits and potatoes were sufficient to support the maximum residue limits. Residues of thiamethoxam and CGA 322704 concentrated in the following human food processed commodities: potato granules (1.2) and potato chips (1.9), however, separate MRLs were not warranted as residues in these were covered under the potato MRL. The magnitude of residues (MORs) in the rotational crops from the confined crop rotation studies triggered the need for field accumulation studies. The predominant residues identified in the soil and rotational crops from the field accumulation study were thiamethoxam and CGA 322704. A plant back interval of 120 days was required on the label for crops not registered for thiamethoxam use. As such, MRLs for rotational crops were not required.

3.5.2 Dietary Risk Assessment

Acute and chronic (cancer and non-cancer) dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM–FCID).

3.5.2.1 Chronic Dietary Exposure Results and Characterization

The following criteria were applied to the intermediate chronic non-cancer analysis for thiamethoxam: 100% crop treated, residues of all crops based on supervised trial median residue (STMdR) values, experimental processing factors (where available), and anticipated residues for all animal commodities. The intermediate chronic dietary exposure from all supported and imported food uses (alone), for all representative population subgroups, is 4.7% to 25.6% of the acceptable daily intake (ADI). The PMRA estimates that aggregate exposure from food and drinking water is considered acceptable, ranging from 5.5% to 26.8% of the ADI for all population subgroups.

The endpoint selected for the chronic dietary risk assessment is protective of any potential cancer findings, for which there are no health risks of concern.

3.5.2.2 Acute Dietary Exposure Results and Characterization

The following assumptions were applied in the basic acute analysis for thiamethoxam: 100% crop treated, Canadian MRLs/American tolerances for all supported and imported food uses, experimental processing factors (where available) and anticipated residues in animal commodities. The basic acute dietary exposure (food alone) is estimated to be < 11% of the ARfD for all population subgroups (95th percentile, deterministic). Aggregate exposure from food and drinking water is considered acceptable, as there is minimal contribution from drinking water.

3.5.3 Aggregate Exposure and Risk

The aggregate risk for thiamethoxam consists of exposure from food and drinking water sources only; there are no residential uses.

3.5.4 Maximum Residue Limits

For the MRLs for this active ingredient, please refer to the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage in the Pesticides section of Canada.ca.

The nature of the residues in animal and plant matrices, analytical methodologies, field trial data, and acute and chronic dietary risk estimates are summarized in Appendix I, Table 1, Table 8 and Table 9.

3.5.5 Concentrations in Drinking Water

The results from the drinking water modelling can be found in ERC2007-01.

4.0 Impact on the Environment

The potential impact on the environment has been reviewed under various separate reviews. For potential impacts to pollinators please refer to PRVD2017-24. For potential impacts to aquatic invertebrates, please refer to PSRD2018-02.

For potential impacts to aquatic organisms (other than invertebrates, including fish, amphibians, algae and aquatic plants) and terrestrial organisms (other than pollinators, including birds, mammals, and other beneficial arthropods), please refer to ERC2007-01. The original review and mitigation for thiamethoxam (Actara products) was presented in ERC2007-01. As a result of this review, additional environmental data was required (including fate, analytical methods, toxicity of transformation products to freshwater invertebrates, additional bee toxicity data, and non-target terrestrial plant toxicity data). The additional data was submitted, reviewed and considered in the risk assessment. Incorporating the new data into the risk assessment resulted in a similar risk profile and mitigation as the original ERC2007-01 assessment for all organisms, except for terrestrial plants. For terrestrial plants there was a terrestrial spray buffer zone implemented.

4.1 Fate and Behaviour in the Environment

A summary of all available information pertaining to the fate and behaviour of thiamethoxam in the environment (excluding drinking water) can be found in PRVD2017-24 and PSRD2018-02, including relevant tables. The environmental fate and behaviour of thiamethoxam are summarized as follows:

Thiamethoxam can come in contact with soil when it is applied directly on the ground, or sprayed on foliage and it washes off onto the ground, or comes into contact with the ground when sprayed on crops. The length of time that thiamethoxam will persist in soil depends on various factors including soil type. In certain fields, thiamethoxam may persist long enough to carryover from one growing season to the next. Major products formed from the microbial degradation of thiamethoxam in soil are CGA 322704 (clothianidin) and CGA 355190, both of which can persist in soil. CGA 322704 has been found in rotational crops.

Thiamethoxam can leach through the soil profile and has been detected in groundwater. CGA 322704 (clothianidin) has been found in both soil pore water and in groundwater. CGA 355190 has been found sporadically in soil pore water but was not detected in groundwater.

Thiamethoxam may enter the aquatic environment through spray drift or runoff. Thiamethoxam readily dissolves in water. In water, thiamethoxam is expected to dissipate relatively quickly if exposed to sunlight. In the absence of sunlight, thiamethoxam will be broken down more slowly by microbes. Thiamethoxam is moderately persistent in aquatic systems.

Thiamethoxam and its transformation product CGA 322704 (clothianidin; also a registered pesticide) are frequently found in surface waters located in Canadian agricultural growing areas.

Major products formed from the break-down of thiamethoxam in water of high pH (alkaline conditions) include CGA 355190 and NOA 404617 (which further breaks down to CGA 309335). The major products CGA 353042 and carbonyl sulfide are formed in the presence of

sunlight. In the presence of microbes, thiamethoxam breaks down to NOA 407475, which is found primarily in sediments.

Residues relevant in the aquatic environment include thiamethoxam, and the major products CGA 353042 and NOA 407475 (both in water and sediment). CGA 355190, NOA 404617 and CGA 309335 may be relevant in alkaline systems; however such conditions are not common in the natural environment. High amounts of carbonyl sulfide are not expected in aquatic systems. CGA 322704 (clothianidin) formed from the breakdown of thiamethoxam in soils can be transported to water bodies through runoff or leaching into groundwater.

4.2 Environmental Risk Characterization

This consultation document references the information in ERC2007-01, as well as recent risk assessments, PRVD2017-24 (for pollinators) and PSRD2018-02 (for aquatic invertebrates).

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

Non-target terrestrial invertebrates

Earthworms
Based on previous assessments (ERC2007-01), thiamethoxam was determined to pose a negligible risk to earthworms.

Bees
Over the past number of years, concerns arose related to the use of thiamethoxam and potential effects to pollinators, and a targeted pollinator re-evaluation was initiated in light of changes to the information required and global updates to the pollinator risk assessment framework. As a result, the PMRA recently completed a targeted pollinator re-evaluation (PRVD2017-24).

Please refer to PRVD2017-24 for risk conclusions and proposed mitigation. In addition, refer to PRVD2017-24 for the science review of the data listed under the Overview, in the section "*Conditionally registered uses and data requirements*" and for the review of public literature relevant to the assessment.

Terrestrial plants
Following the publication of ERC2007-01, non-target terrestrial plant toxicity data was submitted and reviewed. There were no observable effects on the treated plants compared to the untreated control up to 25 g a.i./ha, the highest application rate in the study. Therefore, a NOEC of 25 g a.i./ha was used as the toxicity endpoint for terrestrial plant in the risk assessment of thiamethoxam. A risk to non-target plants cannot be excluded following a direct application at the proposed rates for both Actara 240SC Insecticide and Actara 25WG Insecticide. The size of the terrestrial buffer zone depends on the crop, rate and method of application. Based on the updated risk assessment, mitigation (no-spray terrestrial buffer zones) was added to the label.

Beneficial arthropods
Based on previous assessments (ERC2007-01), thiamethoxam was determined to pose a potential risk to beneficial arthropods other than pollinators. As such, mitigation was placed on the label. It is noted that proposed mitigation following the pollinator re-evaluation may also serve to mitigate potential risk to other beneficial arthropods.

Wild birds
Based on previous assessments (ERC2007-01), thiamethoxam was determined to pose a negligible acute and chronic risk to birds.

Wild mammals
Based on previous assessments (ERC2007-01), thiamethoxam was determined to pose a negligible risk to wild mammals on an acute basis.

4.2.2 Risks to Aquatic Organisms

Non-target aquatic invertebrates
Concerns were identified related to the use of thiamethoxam and potential effects to aquatic invertebrates, and as a result a special review was initiated (REV2016-17). The PMRA recently completed a special review for aquatic invertebrates (PSRD2018-02). Please refer to PSRD2018-02 for risk conclusions and proposed mitigation.

Non-target marine/estuarine invertebrates
Please refer to PSRD2018-02 for risk conclusions and proposed mitigation.

Fish
Based on previous assessments (ERC2007-01), thiamethoxam was determined to pose a negligible acute and chronic risk to fish.

Amphibians
Based on previous assessments (ERC2007-01), thiamethoxam was determined to pose a negligible risk to amphibians.

Aquatic plants and algae
Based on previous assessments (ERC2007-01), thiamethoxam was determined to pose a negligible risk to aquatic organisms such as freshwater algae.

4.2.3 Incident Reports

Since 26 April 2007, registrants have been required by law to report pesticide incidents to the PMRA that are related to their products. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. The USEPA's Ecological Incident Information System (EIIS) was also queried for environmental incidents related to thiamethoxam that were available in that database up to February 2018.

For a summary of incident reports related to aquatic invertebrates, refer to PSRD2018-02.

For aquatic organisms other than invertebrates, there were no incidents for which thiamethoxam was considered to have caused the incident. There was one incident in 2010 in which a pesticide warehouse fire in British Columbia resulted in fish mortality. There were approximately 20 different pesticides that entered the water body as a direct result of the fire douse water (by the fire department) entering the water body. Although thiamethoxam was one of these pesticides, it was unlikely that it contributed to the fish mortality based on the concentrations found in the water samples and corresponding toxicity values. A number of other pesticides which were detected in the water, and considered toxic to fish, were considered to have possibly contributed to the fish mortality.

For a summary of incident reports related to pollinators, refer to PRVD2017-24.

For terrestrial organisms other than pollinators, there were two separate incidents for birds in Canada. Both involved one dead bird (robin and flycatcher) that were possibly killed from exposure to thiamethoxam. There was also one incident involving one dead small mammal that may have been killed from exposure to thiamethoxam. The route of exposure and product were not reported in the incidents.

5.0 Value

Support for pest claims on potato was based on the results of 25 field trials conducted in Canada. Support for pest claims on apple, crab apple, pear and oriental pear for Actara 25WG Insecticide were supported based on the results of 28 field trials conducted in Canada and the United States. Please refer to Section 7 of ERC2007-01, *Thiamethoxam*, for more information.

6.0 Pest Control Product Policy Considerations

6.1 Toxic substance Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, i.e., those that meet all four criteria outlined in the policy: persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*. The *Pest Control products Act* requires that the TSMP be given effect in evaluating the risks of a product.

During the review process, thiamethoxam and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[13] and evaluated against the Track 1 criteria. Thiamethoxam and its end-use products, Actara 25WG Insecticide and Actara 240SC Insecticide did not meet TSMP criteria.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical as well as formulants and contaminants in the end-use products are compared against the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern.*[14] The list is used as described in the PMRA Notice of Intent NOI2005-01[15] and is based on existing policies and regulations including DIR99-03 and DIR2006-02,[16] and taking into consideration the Ozone-depleting Substance

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13 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

14 SI/2005-114

15 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*

16 DIR2006-02, *Formulants Policy and Implementation Guidance Document*

Regulations, 1998, of the *Canadian Environmental Protection Act*, 1999 (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade thiamethoxam and its end-use products do not contain any formulants or contaminants identified in the *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02.

7.0 Summary

7.1 Human Health and Safety

The submitted toxicology database is adequate to characterize the potential health hazards associated with thiamethoxam. In short-term and chronic toxicity studies on laboratory animals, the primary target organs of toxicity were the liver, kidneys, testes, and nervous system. Thiamethoxam was not genotoxic and there was no evidence of carcinogenicity in rats after longer-term dosing. An increase in liver tumours in mice following long-term dosing was associated with the mouse's greater ability, compared to rats and humans, to metabolize thiamethoxam to a hepatotoxic metabolite. A threshold approach was used for the cancer risk assessment as a result. Impaired fetal growth and effects on the fetal skeleton were observed in the presence of maternal toxicity in developmental toxicity studies. In the DNT study, thiamethoxam caused changes in brain morphometry and reductions in brain weight in young animals at a dose level which was slightly toxic to the maternal animal. In reproductive toxicity studies, thiamethoxam produced adverse effects in the testes and sperm of F_1 offspring at non-maternally toxic dose levels. The risk assessment protects against the toxic effects noted above by ensuring that the level of human exposure is well below the lowest dose level at which these effects occurred in animal tests.

Mixers, loaders, applicators handling thiamethoxam and workers re-entering treated areas are not expected to be exposed to levels of thiamethoxam that will result in unacceptable risks when Actara 240SC Insecticide and Actara 25WG Insecticide are used according to label directions.

The personal protective equipment on the product labels is adequate to protect workers.

Residential and bystander exposures are not of concern.

The nature of the residues in plants and animals is adequately understood. The residue definition for enforcement is thiamethoxam and CGA 322704 in plant products and in animal matrices. The proposed use of thiamethoxam on pome fruits and potatoes does not constitute a risk of concern from acute and chronic dietary exposure (food and drinking water) to any segment of the population, including infants, children, adults and seniors. Sufficient crop residue data have been reviewed to recommend MRLs. These may be found in the Maximum Residue Limit Database on the Maximum Residue Limits for Pesticides webpage in the Pesticides section of Canada.ca.

7.2 Environmental Risk

For a summary of the environmental risk to pollinators, refer to PRVD2017-24. For a summary of the environmental risk to aquatic invertebrates, refer to PSRD2018-02.

For potential impacts to aquatic organisms (other than invertebrates, including fish, amphibians, algae and aquatic plants) and terrestrial organisms (other than pollinators, including birds, mammals, and other beneficial arthropods), please refer to ERC2007-01. The original review and mitigation for thiamethoxam (Actara products) was presented in ERC2007-01. As a result of this review, additional environmental data was required (including fate, analytical methods, toxicity of transformation products to freshwater invertebrates, additional bee toxicity data, and non-target terrestrial plant toxicity data). The additional data was submitted, reviewed and considered in the risk assessment. Incorporating the new data into the risk assessment resulted in a similar risk profile and mitigation as the original ERC2007-01 assessment for all organisms, except for terrestrial plants. For terrestrial plants there was a terrestrial no-spray buffer zone implemented.

7.3 Value

Actara 25WG Insecticide and Actara 240SC Insecticide are management tools for use on potato, apple, crab apple, pear and oriental pear to control important insect pests such as aphids on all of these crops, Colorado potato beetle on potato, and plum curculio on the listed tree fruits.

8.0 Proposed Regulatory Decision

With respect to foliar and soil uses of thiamethoxam, Health Canada's PMRA, under the authority of section 8 of the *Pest Control Products Act*, is proposing a three-year registration for the sale and use of the technical grade active ingredient thiamethoxam and the end-use products listed in Table 1. These consultations are carried out under either 28(1)(a) or under 28(1)(c) of the *Pest Control Products Act* (see Table 1 in the Overview). Note that consultations under 28(1)(c) are not subject to subsection 35(1) of the *Pest Control Products Act*.

List of Abbreviations

°C	degree(s) Celsius
µg	microgram
µL	microlitre
a.i.	active ingredient
ADI	acceptable daily intake
AlkP	alkaline phosphatase
ALT	alaminotransferase
ARfD	acute reference dose
AST	aspartate aminotransferase
BrdU	Bromodeoxyuridine
BROD	benzyloxyresorufin-*O*-debenzylase
bw	body weight
bwg	body-weight gain
CAS	Chemical Abstracts Service
cm	centimetre
DFR	dislodgeable foliar residue
DT_{50}	dissipation time 50% (the time required to observe a 50% decline in concentration)
DT_{75}	dissipation time 75% (the time required to observe a 75% decline in concentration)
DT_{90}	dissipation time 90% (the time required to observe a 90% decline in concentration)
dw	dry weight
EC_{05}	effective concentration on 5% of the population
EC_{10}	effective concentration on 10% of the population
EC_{25}	effective concentration on 25% of the population
EC_{50}	effect concentration on 50% of the population
EEC	expected environmental concentration
ER_{25}	effective rate on 25% of the population
ER_{50}	effective rate on 50% of the population
EROD	ethoxyresorufin-*O*-deethylase
EXAMS	Exposure Analysis Modeling System
F_0	parental generation
F_1	first filial generation
F_2	second filial generation
FC	food consumption
FIR	food ingestion rate
fw	fresh weight
g	gram
GGT	gamma glutamyl transferase
GLC	gas liquid chromatography
ha	hectare
HAFT	highest average field trial
Hb	hemoglobin
Hct	hematocrit

HDW	red blood cell distribution width
HPLC	high performance liquid chromatography
HPLC-MS	high performance liquid chromatography with mass spectrometry
HPLC-MS/MS	high performance liquid chromatography with tandem mass spectrometry
HPLC-UV	high performance liquid chromatography with ultraviolet detection
Ht	hematocrit
1/n	exponent for the Freundlich isotherm
ILV	independent laboratory validation
iNOS	inductible nitric oxide synthase
kg	kilogram
K_d	adsorption coefficient
K_F	Freundlich adsorption coefficient
K_{oc}	organic carbon partition coeffient
K_{ow}	*n*-octanol–water partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
LR_{50}	lethal rate 50%
LOAEL	lowest observed adverse effect level
LOEC	no observed effect concentration
LOQ	limit of quantitation
m	metre
MAS	maximum average score
MATC	maximum acceptable toxicant concentration
MCV	mean cell volume
MCH	mean cell hemoglobin
mg	milligram
MIS	maximum irritation score
mL	millilitre
MMAD	mass median aerodynamic medium
MOE	margin of exposure
mol	molar
MRL	maximum residue limit
MS	mass spectrometry
N/A	not applicable
NQ	not quantifiable
nm	nanometre
NO	nitric oxide
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
N/R	not required
OC	organic carbon content
OM	organic matter content
Pa	Pascal
PBI	plantback interval
PHI	plantharvest interval

PHED	Pesticide Handlers Exposure Database
p*K*a	dissociation constant
ppm	parts per million
PMRA	Pest Management Regulatory Agency
PROD	pentoxyresorufin-*O*-depentylase
PRZM	Pesticide Root Zone Model
RBC	red blood cell
RQ	risk quotient
SDEV	standard deviation
$t_{1/2}$	half-life
TSMP	Toxic Substances Management Policy
TRR	total radioactive residue
UF	uncertainty factor
USEPA	United States Environmental Protection Agency
UV	ultraviolet
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Residue Analysis

Parameters	Plant matrices		Animal matrices
Method ID	AG-675	MS-269	AG-675
Type	Data-gathering and Enforcement	Data-gathering	Data-gathering and Enforcement
Analytes	Thiamethoxam and CGA 322704	Thiamethoxam and CGA 322704	Thiamethoxam and CGA 322704
Instrumentation	HPLC-UV or HPLC-MS	HPLC-MS/MS	HPLC-UV or HPLC-MS
LOQ	0.01 ppm for all crop matrices except fruit juices (0.005 ppm), grass (0.05 ppm) and cured tobacco (<0.1 ppm)	0.01 ppm for each analyte	0.01 ppm in meat, poultry and eggs and 0.005 ppm in milk
ILV	Successfully validated by ILV	Successfully validated by ILV	Successfully validated by ILV in eggs, milk and beef liver
Radio validation	Adequately radio validated	None	Adequately radio validated

Table 2 Select Thiamethoxam Metabolites

Syngenta Code	Chemical Name (IUPAC)
CGA265307	*N*-(2-Chlorothiazol-5-ylmethyl)-*N'*-nitroguanidine
CGA322704	*N*-(2-Chlorothiazol-5-ylmethyl)-*N'*-methyl-*N''*-nitroguanidine
CGA330050	3-(2-Chlorothiazol-5-ylmethyl)-[1,3,5]-oxadiazinan-4-ylidene-N-nitroamine
CGA353968	1-(2-Chlorothiazol-5-ylmethyl)-3-methylurea
R6	2-Acetylamino-3-[5-(5-methyl-4-nitroimino[1,3,5]oxadiazinan-3-ylmethyl)-thiazol-2-ylsulfanyl]-propionic acid

Table 3 Toxicology Profile of Technical Thiamethoxam (CGA 293343)

NOTE: Effects noted below are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons. Effects on organ weights are known or assumed to reflect changes in absolute weight and relative (to bodyweight) weight unless otherwise noted. Effects above the LOAEL(s) have not been reported in this table for most studies for reasons of brevity.

Study Type/Species/PMRA No.	Study Results
Toxicokinetic Studies	
The absorption, distribution, metabolism, and excretion of thiamethoxam were investigated in rats and mice. Tif:RAIf rats (♂/♀) received gavage doses of thiamethoxam labelled with ^{14}C on either the oxadiazine or thiazole ring as a single low (0.5 mg/kg bw) dose, a single high (100 mg/kg bw) dose or as a single low dose following pre-treatment with unlabelled test material at the low dose for two wks. Additional animals received the low dose via a single intravenous administration. Biliary excretion was also assessed in animals that were bile duct-cannulated. Thiamethoxam was rapidly and extensively absorbed and widely distributed to tissues. Blood concentrations peaked within 4 hrs of dosing. Highest tissue	

Study Type/Species/PMRA No.	Study Results
	concentrations were detected in skeletal muscle. Elimination was rapid; within 24 hrs of dosing, the majority of radioactivity (84–95% of the AD) was excreted in urine, with smaller amounts in the feces. Less than 0.2% of the AD was detected in expired air. Half-lives of elimination from tissues ranged from 2–6 hrs and residues in tissues 7 days post-dosing were low. Unchanged thiamethoxam accounted for most (69–83%) of the AD excreted in urine; only two metabolites, CGA322704 and CGA265307, accounted for 5–13% and up to 2% of the AD, respectively. There were fewer fecal metabolites isolated; however, the main constituents paralleled those found in urine. Biliary metabolites were fewer, but the main constituents were unchanged thiamethoxam and CGA322704. There were no significant differences in absorption, distribution, profile of metabolites, or excretion between sexes, or among the dosing regimens. (PMRA No. 1178128, 1178129, 1178149) MAG Tiflbm:MAG mice (♂) received gavage doses of thiamethoxam labelled with ^{14}C on the thiazole ring daily for 14 days by gavage at a dose level of 118 mg/kg bw/day. Thiamethoxam was rapidly excreted, predominantly in the urine. Approximately 72% of the AD was excreted in the urine, and 19% was excreted in the feces. A small but measurable amount was detected in expired air (approximately 0.2% of the AD). A large number of metabolites were isolated from the urine and feces; however, only three constituents in urine accounted for a significant amount of the AD. The predominant constituent was unchanged thiamethoxam, accounting for 33–41% of the AD. The two principal metabolites were CGA322704 (8–12% of the AD) and CGA265307 (9–18% of the AD). One additional significant metabolite (R6, approximately 2% of the AD) was isolated from feces. (PMRA No. 1178132) TIF:MAG mice (♂) received dietary administration of thiamethoxam radiolabelled with ^{14}C on the oxadiazine ring for 29 days at dose levels of 0, 17, 81, or 364 mg/kg bw/day. Animals received a gavage dose of 20 mg/kg bw radiolabelled test material one day after the end of this dosing period. A second radiolabelled dose was administered 72 hrs after this dose. Absorption (based on urinary excretion) was approximately 70% regardless of dose level. Approximately 70% of the AD was excreted via urine over a 72-hr period, with fecal excretion accounting for the remainder regardless of dose level. The majority of urinary and fecal excretion occurred within 24 hrs of dosing. Unchanged thiamethoxam accounted for the majority of urinary radioactivity, while both CGA322704 and CGA265307 (main urinary and fecal metabolites) and CGA353968, (minor urinary and fecal metabolite) were present. In plasma 6 hrs post-dosing, CGA265307 was the major metabolite (43–55% of radioactivity in plasma) and unchanged thiamethoxam and metabolite CGA322704 accounted for 17–26%, and 20–26% of plasma radioactivity, respectively. Bile contained low levels of unchanged thiamethoxam, CGA265307 and CGA322704, whereas a metabolite called R6 accounted for 15–22% of the AD. Metabolic profiles in bile and plasma samples were not impacted by dose level. Liver contained low levels of unchanged thiamethoxam, CGA265307 and CGA322704 at 6 hrs post-dosing. (PMRA No. 859906) ^{14}C-radiolabelled (oxadiazine ring) thiamethoxam was administered to ♂ TiF:MAG mice and ♂ Tif:RAI rats by gavage at a dose of 100 mg/kg bw and animals were sacrificed at several intervals up to 24 hrs post-dosing. Maximum blood concentrations were reached at 0.5 hrs (mice) and 6 hrs (rats) after administration. Half-lives of elimination from blood were 4 (mice) and 3 (rats) hrs. Unchanged thiamethoxam was the major component in blood extracts (78% mice, 82% rats). In mice, CGA322704, CGA265307 and CGA330050 were detected at comparable levels (10–15%). In rats, CGA322704 was detected in blood (16%) with only trace amounts of CGA265307 (0.3%). CGA330050 was not detected. (PMRA No. 859910, 859911) Tif:RAIf rats (♂) and Tif:MAG mice (♂) received ^{14}C-radiolabelled thiamethoxam (oxadiazine ring) via diet at dose levels of 2500 (mice) and 3000 (rats) ppm for 1 or 10 wks. Thiamethoxam and metabolites CGA322704, CGA265307 and CGA330050 were evenly distributed between red blood cells and

Study Type/Species/PMRA No.	Study Results
plasma. A species difference in metabolism was observed. In mice, the plasma concentrations of thiamethoxam declined and those of CGA322704 and CGA265307 increased with increased duration of dosing, whereas in rats, thiamethoxam concentrations in plasma increased approximately 2.7-fold and those of the metabolites decreased with extended dosing. After 10 wks of dietary administration, CGA265307 was present in mouse plasma at 108-fold higher concentrations than in rat plasma. (PMRA No. 859909) Liver fractions extracted from rat, mouse and human tissue preparations were used to compare the in vitro liver metabolism of thiamethoxam across species. Depending on the metabolism pathway involved (either via oxidative loss of the oxadiazine ring to form CGA322704 or via oxidative N-demethylation to form CGA330050), metabolic rates in mouse liver were 54-fold (via CGA322704) and 87-fold (via CGA330050) higher than those in rat liver and 371-fold and 238-fold higher respectively than those in human liver. (PMRA No. 859909) ^{14}C-radiolabelled thiamethoxam (oxadiazine ring) was administered by gavage to Tif:MAG mice (♂/♀) as a single dose of 0.5, or 100 mg/kg bw with sacrifice 3 days later. Absorption was high (74–93% of the AD) and was similar between sexes and dose groups and did not appear to be saturated at the high dose. At the low dose, tissue residues 72 hrs following administration were low with highest amounts in liver. At the high-dose, residues in tissues 72 hrs post-dosing were about 200-times higher corresponding to the 200-fold increase in dose. Liver showed the highest residue levels. ♀ retained greater quantities of radioactivity than ♂. For all dose groups, total body radioactivity was ≤ 1% of AD at the 72-hr sacrifice. (PMRA No. 859907) ^{14}C-radiolabelled thiamethoxam (oxadiazine ring) was administered as a single gavage dose at 0.5 or 100 mg/kg bw to Tif:MAG mice (♂/♀) with sacrifice 3 days later. Metabolite patterns in urine and feces were independent of sex and dose. Unchanged thiamethoxam was the major component in excreta accounting for 28–44% of the AD. Major metabolites in excreta were CGA265307 and CGA322704 accounting for 16–22% and 12–18% of the AD, respectively. (PMRA No. 859908) In a special metabolism study, plasma and liver metabolites of thiamethoxam in rats and mice were compared after dietary administration for 1 wk up to 50 wks. Blood and liver samples from several dietary studies were used for this study. After 50 wks of thiamethoxam administration, concentrations of thiamethoxam in plasma were relatively similar in both species whereas the concentrations of metabolites were noticeably greater in mouse plasma than in rat plasma. The concentrations of CGA 265307 were approximately 22-fold greater in mouse plasma than in rat plasma after 1 wk of administration. After 10 wks administration, the concentration of CGA 265307 in mouse plasma had increased approximately 3.6-fold compared to after 1 wk of administration, whereas that in rat plasma had reduced. Plasma concentrations of CGA265307 and CGA330050 were up to 140-fold and 15-fold greater, respectively, in mice than rats. In Tif:MAG and CD-1 mice fed a diet containing 2000 ppm of the metabolite CGA322704 for up to 20 wks, only CGA322704 and CGA265307 were detected in plasma. The major difference between the metabolism of rats and mice is the production of metabolite CGA330050 in mice. (PMRA No. 859912)	
Acute Toxicity Studies	
Oral Mice, CD-1 PMRA No. 1178092	LD_{50} = 783/964 mg/kg bw ♂/♀ Combined LD_{50} = 871 mg/kg bw All deaths occurred within 1 day of dosing. Clinical signs noted on the day of dosing included clonic convulsions, ↓ spontaneous movement or prone position. Bwg was ↓ in surviving ♀ on the day following dosing.

Study Type/Species/PMRA No.	Study Results
	Moderately toxic.
Oral Rats, Sprague-Dawley PMRA No. 1178091	LD_{50} = 1563 mg/kg bw All deaths occurred within 6 hrs of dosing. Clinical signs noted on the day of dosing included ptosis, ↓ spontaneous movement and tonic convulsions. Bwg was ↓ for 2 days following dosing in all animals. Slightly toxic.
Oral (Metabolite CGA322704) Rats, Sprague-Dawley PMRA No. 1178093	LD_{50} > 2000 mg/kg bw No mortalities occurred. Clinical signs included tremors, piloerection, and hunched posture in all animals that recovered by day 1. Low toxicity.
Dermal Rats, Sprague-Dawley PMRA No. 1178094	LD_{50} > 2000 mg/kg bw No mortalities, clinical signs of toxicity or effects on bw. Low toxicity.
Inhalation (nose-only) Rats, Sprague-Dawley PMRA No. 1178095	LC_{50} > 3.72 mg/L No mortality or clinical signs of toxicity. Slightly ↓ bw in 2 high-dose ♀ on study day 7, recovery noted by day 14. Low toxicity.
Eye irritation Rabbits, Japanese White PMRA No. 1178096	MAS = 0 MIS = 10.0 (1 hr) Slight conjunctival redness and swelling observed at 1 hr with eye closure and more than normal discharge. All signs of irritation absent at 24 hrs. Minimally irritating.
Skin irritation Rabbits, Japanese White PMRA No. 1178097	MAS = 0 MIS = 0 No signs of irritation in any of the animals tested. Non-irritating.
Skin sensitization (Maximization) Guinea pigs, Pirbright White PMRA No. 1178099	Not a dermal sensitizer.
90-day oral (dietary) Mice, Tif:MAGf	NOAEL = 14/19 mg/kg bw/day ♂/♀ LOAEL = 176/231 mg/kg bw/day ♂/♀

Study Type/Species/PMRA No.	Study Results
PMRA No. 1178100, 1178101	Effects at LOAEL: ↑ hepatocellular hypertrophy; ↓ kidney wt (♂).
28-day oral (gavage), range-finding Rats, Tif:RAlf, ♂ PMRA No. 1178137	NOAEL not established as this is a range-finding study. 100 mg/kg bw/day: hyaline change of renal tubular epithelium (not present in high-dose animals); ≥ 300 mg/kg bw/day: ↑ liver wt, dilatation of renal pelvis, hepatocellular hypertrophy, ↑ adrenocortical fatty change; 1000 mg/kg bw/day: ↓ bwg, ↓ plasma protein, ↑ AST, ALP and GGT, ↓ thymus wt.
28-day oral (dietary) Rats, Tif:RAlf PMRA No. 1178135, 859918	NOAEL = 8.0/211 mg/kg bw/day ♂/♀ LOAEL = 82/763 mg/kg bw/day ♂/♀ Effects at LOAEL: minimal to moderate hyaline change of renal tubular epithelium, basophilic proliferation of renal tubules, minimal to moderate dilatation of renal pelvis (♂);↓ bw and fc, ↑ cholesterol, urea and sodium, ↑ liver wt, minimal to marked hepatic cell hypertrophy, minimal to moderate fatty change of adrenal cortex, ↑ absolute kidney wt, ↑ relative adrenal wt, minimal and focal cholangiofibrosis of intrahepatic bile ducts, minimal hepatocellular hypertrophy, minimal dilatation of renal pelvis, hypertrophy of thyroid follicular epithelium (♀). Treatment of ♂ resulted in an ↑ accumulation of renal alpha 2u-globulin. Similar findings were not observed in treated ♀ or control animals of either sex.
90-day oral (dietary) Rats, Tif:RAlf PMRA No. 1178103, 859915	NOAEL = 1.7/93 mg/kg bw/day ♂/♀ LOAEL = 18/182 mg/kg bw/day ♂/♀ Effects at LOAEL: minimal to marked hyaline change in renal tubular epithelium, ↑ incidence of chronic tubular lesions, slight to marked renal pelvic dilatation (♂); ↓chloride, ↓ sodium, minimal lymphohistiocytic infiltration of the liver parenchyma, ↑ incidence of chronic tubular lesions and ↑ severity of nephrocalcinosis, extramedullary hematopoiesis in spleen, minimal to moderate fatty change in the adrenal cortex (♀). Treatment of ♂ at 5000 ppm resulted in a slightly ↑ accumulation of renal alpha 2u-globulin. Similar findings were not observed in treated ♀ or control animals of either sex.
28-day oral (dietary) Dogs, Beagle PMRA No. 1178154	NOAEL not established (2/sex/dose level) 48/43 mg/kg bw/day (HDT): ↓ bw and fc, ↑ urea, ↓ thymus wt, minimal accumulation of pigment within hepatic Kupffer cells, minimal to moderate atrophy of splenic white pulp-marginal zone, minimal to marked thymic atrophy; ↑ Hct, Hgb and RBC, leukopenia, ↑ ALT, ↑ thyroid wt (♂); ↓ WBC counts, ↑ creatinine, ↓ absolute brain wt (♀).
90-day oral (dietary)	NOAEL = 8.2/9.3 mg/kg bw/day ♂/♀

Study Type/Species/PMRA No.	Study Results
Dogs, Beagle PMRA No. 1178104	LOAEL = 32/34 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ prothrombin time, ↓ calcium and A/G ratio, ↓ ALT; ↓ cholesterol and phospholipids (♂); ↓ albumin (♀)
12-month oral (dietary) Dogs, Beagle PMRA No. 1178105	NOAEL = 4.1/4.5 mg/kg bw/day ♂/♀ LOAEL = 21/25 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ creatinine and urea, ↓ ALT; atrophy of seminiferous tubules (♂); transient ↓ in fc (♀)
28-day dermal Rats, Tif:RAlf PMRA No. 1178136	NOAEL = 250/60 mg/kg bw/day ♂/♀ LOAEL = 1000/250 mg/kg bw/day ♂/♀ Effects at LOAEL: slightly ↓ bw, minimal tubular hyaline change in kidneys (♂); ↑ glucose and ALP, minimal inflammatory cell infiltration in the liver, minimal hepatocellular degeneration (♀)
78-wk oral (dietary) Mice, Tif:MAGf PMRA No. 1178113, 1178114	NOAEL = 2.6/3.7 mg/kg bw/day ♂/♀ LOAEL = 64/88 mg/kg bw/day ♂/♀ Effects at LOAEL: hepatocellular hypertrophy, foci of cellular alteration, necrosis of single hepatocytes, ↑ mitotic activity, inflammatory cell infiltration, pigment deposition; Kupffer cell hyperplasia (♂); ↑ liver wt, ↑ incidence of hepatocellular adenomas (♀); ≥ 162/215 mg/kg bw/day: ↑ incidence of hepatocellular adenocarcinomas; ↑ liver wt, ↑ incidence of hepatocellular adenomas (♂); 354/479 mg/kg bw/day: ↑ incidence of hepatocellular hypertrophy, necrosis of single hepatocytes, inflammatory cell infiltration and Kupffer cell pigmentation (9-month interim sacrifice), ↓ bw and bwg, extramedullary hematopoiesis in spleen, epithelial hyperplasia in glandular stomach. At dose levels of 0/0, 0.7/0.9, 2.6/3.7, 64/88, 162/215 or 354/479 mg/kg bw/day, respectively in ♂/♀: Hepatocellular adenoma ♂: 11/50[a], 5/50, 10/49, 17/50, 27/50**, 40/50** ♀: 0/50[a], 0/50, 0/50, 5/50*, 8/50**, 31/50** (HC range: ♂ 10-46%; ♀ 0-8%) Hepatocellular carcinoma ♂: 1/50[a], 4/50, 2/50, 5/50, 7/50*, 20/50** ♀: 0/50[a], 0/50, 0/50, 0/50, 2/50, 11/50** (HC range: ♂ 0-24%; ♀ 0–2%) Combined (adenoma or carcinoma) ♂: 12/50[a], 7/50, 12/50, 19/50, 27/50**, 45/50** ♀: 0/50[a], 0/50, 0/50, 5/50*, 9/50**, 32/50** * $p<0.05$ compared to control ** $p<0.01$ compared to control [a] denotes a linear trend, $p<0.01$

Study Type/Species/PMRA No.	Study Results
	Evidence of oncogenicity.
2-yr oral (dietary) Rats, Tif:RAlf PMRA No. 1178121, 1178122, 1178123, 859916, 859917	NOAEL = 21/50 mg/kg bw/day ♂/♀ LOAEL = 63/155 mg/kg bw/day ♂/♀ Effects at LOAEL: slightly ↑ wc, ↑ incidence of lymphocytic infiltration in kidneys and chronic nephropathy (♂);↓ bwg, ↑ incidence of foci of cellular alteration in liver, ↑ incidence of chronic tubular lesions in kidneys (♀); No evidence of oncogenicity. Treatment of ♂ at 1500 ppm for 52 weeks or 2 years resulted in a slightly ↑ accumulation of renal alpha 2u-globulin. Similar findings were not observed in treated ♀ or control animals of either sex.
Bacterial reverse mutation PMRA No. 1178144	Negative in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537, and in E. Coli WP2uvrA with and without metabolic activation.
Bacterial reverse mutation PMRA No. 1188411	Negative in *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 with and without metabolic activation.
In vitro chromosome aberrations PMRA No. 1178145	Negative in Chinese hamster V79 cells with and without metabolic activation.
In vitro unscheduled DNA synthesis PMRA No. 1178148	Negative in primary hepatocytes from Tif:RAlf rats with and without metabolic activation.
In vitro chromosome aberrations PMRA No. 1178146	Negative in Chinese hamster ovary cells (CCL 61) with and without metabolic activation.
In vivo bone marrow micronucleus PMRA No. 1178147	Negative in Tif:MAGf Mice with and without metabolic activation.
Range-finding oral (dietary) reproduction Rats, Tif:RAlf PMRA No. 1178127	NOAEL not established as this is a range-finding study. ≥ 75 mg/kg bw/day: ↓ bwg during pre-mating period (♀); ≥ 126/136 mg/kg bw/day : ↓ fc during pre-mating period; 241/275 mg/kg bw/day (highest dose level tested): ↓ bwg during pre-mating period (♂); ↓ bwg during lactation (♀).
Oral (dietary) two-generation reproduction Rats, Tif:RAlf	Parental Toxicity NOAEL = 1.8/202 mg/kg bw/day ♂/♀ LOAEL = 61/not determined (HDT) ♂/♀ Effects at LOAEL: ↑ incidence of hyaline change in renal tubules (F_0 and

Study Type/Species/PMRA No.	Study Results
PMRA No. 1178124,1178125, 1178126, 1178143, 1063161, 1996080, 1997353	F_1) and renal tubular casts (F_0) (♂); 158/202 mg/kg bw/day: slightly ↓ bwg (F_0 and F_1), ↑ incidence of renal tubular casts (F_1) (♂); hyaline change in renal tubules (1 F_1 ♀) (♀). Offspring Toxicity NOAEL = 2.4 mg/kg bw/day LOAEL = 79 mg/kg bw/day Effects at LOAEL: ↓ bw and bwg (F_{2a} and F_{2b}, PNDs 7, 14 and/or 21) (♀); 202 mg/kg bw/day: ↓ bw and bwg (F_{1a}, F_{1b}, F_{2a} and F_{2b} PNDs 7, 14 and/or 21). Reproductive Toxicity NOAEL = 0.6/79 mg/kg bw/day ♂/♀ LOAEL = 1.8/202 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ incidence and severity of atrophy of the seminiferous tubules in the testes (F_1: 6/30, 8/30, 15/30, 24/30 and 14/30 at 0, 10, 30, 1000 and 2500 ppm) (♂); slightly ↓ mean litter sizes at birth (F1a and F1b) (♀); 158 mg/kg bw/day: ↓ absolute testicular wts (F_1) (♂). Evidence of sensitivity of the young (testis effects observed only after in utero and postnatal exposure). Equivocal results in sperm motility (↓ at all dose levels tested with no apparent dose-relationship), evaluated further in a separate, complementary study that revealed no effect of treatment on sperm motility; however, the study was conducted only on F_0 animals whereas seminiferous tubule atrophy was observed in F_1 animals.
Complementary study: Investigation on sperm cells (10-wk dietary) Rats, Tif:RAlf PMRA No. 1178125	Supplemental 165 mg/kg bw/day (HDT): ↓ bw, ↓ bwg, ↓ fc. No treatment-related effects on total number of testicular sperm cells or sperm cell concentration in cauda epididymis luminal fluid, epididymal sperm motility, or sperm morphology.
Oral (dietary) two-generation reproduction Rats, Tif:RAlf PMRA No. 859896 to 859905	Parental Toxicity NOAEL = 3.0/3.1 mg/kg bw/day ♂/♀ LOAEL = 62/62 mg/kg bw/day ♂/♀ Effects at LOAEL: ↑ incidence of renal tubular casts and hyaline droplets (F_0 and F_1) (♂); ↓ absolute pituitary wt (15%) (F_0) (♀); 156/159 mg/kg bw/day: ↑ relative liver wts (F_1); ↓ bw, bwg and fc (F_0), ↑ relative adrenal and kidney wts (F_0), ↑ adrenal cortex hyperplasia (F_0) (♂). Offspring Toxicity

Study Type/Species/PMRA No.	Study Results
	NOAEL = 62/62 mg/kg bw/day ♀ LOAEL = 156/159 mg/kg bw/day ♀ Effects at LOAEL: pup deaths (wks 3–4), ↓ litter wt (F_1 and F_2, during lactation); delayed preputial separation (F_2 ♂). Reproductive Toxicity NOAEL = 1.2/159 mg/kg bw/day ♂/♀ LOAEL = 3.0/not determined (HDT) ♂/♀ Effects at LOAEL: ↓ total sperm and number of sperm/gram of testes wt (F_1) (♂); ≥ 62 mg/kg bw/day: ↑ relative epididymides and testes wts (F_1) (♂); 156 mg/kg bw/day: slightly delayed preputial separation (F_1), ↑ absolute epididymides wt (F_1), ↑ seminal vesicle wt (F_0), ↑ sperm with reduced straight line, curvilinear, and average path velocities (F_1), ↑ incidence of abnormal sperm (F_0), minimal germ cell loss/disorganization and Sertoli cell vacuolation in testes (F_1) (♂). Evidence of sensitivity of the young (sperm effects observed only after in utero and post-natal exposure).
Range-finding oral (gavage) developmental toxicity Rats, Tif:RAlf PMRA No. 1178116, 1178117	NOAEL not established as this is a range-finding study. Maternal Toxicity: ≥ 500 mg/kg bw/day: ↓ bwg (during first half of dosing), ↓ fc (during dosing); 1000 mg/kg bw/day: ↓ bw (during first half of dosing), piloerection, hypoactivity and hunched posture (during dosing). Developmental Toxicity: 1000 mg/kg bw/day: ↓ fetal bw.
Oral (gavage) developmental toxicity Rats, Tif:RAlf PMRA No. 1178115	Maternal Toxicity: NOAEL: 30 mg/kg bw/day LOAEL: 200 mg/kg bw/day Effects at LOAEL: ↓ bwg (during first half of dosing), ↓ fc (during dosing); Developmental Toxicity: NOAEL: 200 mg/kg bw/day LOAEL: 750 mg/kg bw/day Effects at LOAEL: ↓ fetal bw, ↑ incidence of skeletal findings (asymmetrically shaped sternebrae 6 and irregular ossification of the occipital bone).

Study Type/Species/PMRA No.	Study Results
	Developmental toxicity in the presence of maternal toxicity.
Range-finding oral (gavage) developmental toxicity Rabbits, Russian Chbb:HM PMRA No. 1178119, 1178120	NOAEL not established as this is a range-finding study. Maternal Toxicity: ≥ 50 mg/kg bw/day: ↓ bwg and fc (during dosing); ≥ 150 mg/kg bw/day: ↓ bw (during dosing), ↓ mean gravid uterus wt; 500 mg/kg bw/day: all dams died between GDs 10 and 16. Developmental Toxicity: ≥ 150 mg/kg bw/day: ↓ fetal bw.
Oral (gavage) developmental toxicity Rabbits, Russian Chbb:HM PMRA No. 1178118	Maternal Toxicity: NOAEL = 50 mg/kg bw/day LOAEL = 150 mg/kg bw/day Effects at LOAEL: 3 unscheduled deaths, hemorrhagic uterine contents, hemorrhagic discharge in the perineal area, ↓ bw (during dosing), ↓ fc (during dosing), ↑ post-implantation loss. Developmental Toxicity: NOAEL = 50 mg/kg bw/day LOAEL = 150 mg/kg bw/day Effects at LOAEL: ↓ fetal bw, slightly ↑ incidence of skeletal findings (fused or asymmetrically shaped sternebrae) - not statistically significant, ↑ on fetal basis only, and slightly outside of the upper end of the HC range). Developmental toxicity in the presence of maternal toxicity.
Acute oral (gavage) neurotoxicity Rats, Sprague-Dawley PMRA No. 1178165	NOAEL = 100 mg/kg bw LOAEL = 500 mg/kg bw Effects at LOAEL: drooped palpebral closure, ↓ rectal temperature, ↑ forelimb grip strength and ↓ locomotor activity; No evidence of neuropathology.
13-wk oral (dietary) neurotoxicity Rats, Sprague-Dawley PMRA No. 1178133	NOAEL = 95/216 mg/kg bw/day ♂/♀ (HDT) There were no treatment-related systemic or neurological effects observed in this study.
Range-finding Oral (dietary) Developmental Neurotoxicity Rats, Alpk:APfSD	NOAEL not established as this is a range-finding study. Maternal: 213 mg/kg bw/day: ↓ bw (slight at this dose level; during gestation) and fc (GD11–18, PND 8–11);

Study Type/Species/PMRA No.	Study Results
PMRA No. 1036615	362 mg/kg bw/day: ↓ bw and fc (during gestation and lactation). Offspring: 213 mg/kg bw/day: ↓ pup bw (at birth); ↓ bwg (PND 15 and 22) (♂). 362 mg/kg bw/day: ↓ pup bw and bwg (at birth and throughout the postnatal period).
Oral (dietary) developmental neurotoxicity Rats, Alpk:APfSD PMRA No. 1036606 to 1036611, 1036617 to 1036621	Maternal Toxicity NOAEL = 35 mg/kg bw/day LOAEL = 298 mg/kg bw/day Effects at LOAEL: ↓ bw, bwg and fc (during gestation and lactation). Offspring Toxicity NOAEL = 35 mg/kg bw/day LOAEL = 298 mg/kg bw/day Effects at LOAEL: ↓ pup bw, ↓ absolute brain wt (PND 12), significantly ↓ dorsal cortex thickness, thalamus width, thalamus/cortex overall width and hippocampus width (PND 63); ↓ absolute brain wt (PND 63), significantly ↓ molecular layer of the cerebellum and the cerebellum length (PND 12), delayed sexual maturation, significantly ↓ piriform cortex thickness, corpus callosum thickness and thalamus height (PND 63) (♂); significantly ↓ thalamus width (PND 12) (♀). Serious effects in the young in the presence of maternal toxicity.
Effects on biochemical parameters in the liver, 14-day dietary study Mice, Tif:MAGf PMRA No. 1178140	20 mg/kg bw/day: slightly ↑ PROD and BROD activity (♀); ≥ 74/92 mg/kg bw/day: ↑ PROD and BROD activity; slightly ↑ PROD and BROD activity (♂); slightly ↑ EROD activity (♀); 367/486 mg/kg bw/day: slightly ↑ liver wts, moderate ↑ in cytochrome P450 content, slight to moderate ↑ in activity of several microsomal enzymes, slightly ↑ cytosolic glutathione-S-transferase; ↑ PROD and BROD activity (♂); slightly ↑ microsomal protein content in liver (♀).
Assessment of hepatic cell proliferation, dietary study (3, 7, 13, 27 or 59 days) Mice, Tif:MAGf PMRA No. 1178141	20 mg/kg bw/day: ↑ BrdU labelling index (day 7) (♀); 72/87 mg/kg bw/day: ↑ BrdU labelling index (♂: days 13, 27 and 59; ♀: days 7 and 13); 386/463 mg/kg bw/day: ↑ liver wts, speckled liver, hepatocellular glycogenesis/fatty change, hepatocellular necrosis, apoptosis and pigmentation at 59 days, ↑ BrdU labelling index (days 3, 7, 13 and 59).
Determination of induction of liver enzymes, dietary study (7, 14, 28 or 60 days) Mice Tif:MAG ♂	≥ 448 mg/kg bw/day: slightly ↓ cytosolic protein content (28 days), slightly ↓ glutathione reductase activity (60 days), ↑ glutathione S-transferase activity and γ-glutamylcysteine synthetase activity (all timepoints);

Study Type/Species/PMRA No.	Study Results
PMRA No. 859919	976 mg/kg bw/day: slightly ↓ cytosolic protein content (60 days).
Determination of parameters indicative for oxidative stress, dietary study (7, 14, 28 or 60 days) Mice, Tif:MAG ♂ PMRA No. 859920	No treatment-related mortalities or clinical signs of toxicity were noted. ≥ 448 mg/kg bw/day: slightly ↑ mean free 8-isoprostane F2α in plasma (day 14 onwards), ↑ mean hepatic concentration of reduced glutathione (all timepoints); 976 mg/kg bw/day: ↓ final bw, ↓ bwg (throughout study), slightly ↓ mean 8-isoprostane F2α concentration in the liver (7 days), slightly ↓ mean hepatic concentration of oxidized glutathione (at 28 days). There was no indication of oxidative stress in the livers of treated mice, as indicated by little change in antioxidants (α-tocopherol) or indicators of peroxidation (oxidized glutathione and malondialdehyde).
Comparative hepatotoxicity of thiamethoxam in weanling (21-day old) and adult mice, 7-day dietary study Mice, Tif:MAG ♂ PMRA No. 859925	There were no mortalities, clinical signs of toxicity, and effects on body weight or alterations in plasma levels of liver enzymes in adult or weanling mice noted in this study. Adults: ≥ 62 mg/kg bw/day: ↓ cholesterol levels; 314 mg/kg bw/day: centrilobular vacuolation and ↓ eosinophilia of the liver. Weanlings: ≥ 151 mg/kg bw/day: ↓ cholesterol levels; 314 mg/kg bw/day: centrilobular vacuolation and ↓ eosinophilia of the liver (same frequency but less severe than that noted in adults). Concentrations of thiamethoxam and CGA265307, CGA322704 and CGA330050 were higher in all weanling animals compared to adults but without increased liver toxicity.
Histochemical assessment of hepatic apoptosis, dietary study (3, 7, 13, 27, 59 days, 9 months) Mice, Tif:MAG ♂ PMRA No. 859914	In this retrospective examination, the following was noted from dietary studies in mice of various durations: ≥ 25 mg/kg bw/day: significantly ↑ numbers of apoptotic figures, mostly localized centrilobularly often adjacent to central veins (after 59 days); 314 mg/kg bw/day: significantly ↑ numbers of apoptotic figures, mostly localized centrilobularly, often adjacent to central veins (after 9 months).
Comparative hepatotoxicity of metabolites in 2 different strains of mice, dietary study (1, 10, 20 wks) Mice, Tif:MAGf and CD-1 ♂	Animals received 0 or 2500 ppm thiamethoxam (~0 or 314 mg/kg bw/day), 2000 ppm CGA322704, or 500 ppm CGA265307 for up to 20 wks. There were no treatment-related clinical signs of toxicity, effects on hematology, macroscopic findings or mortalities noted in this study. No ↑ in BrdU labelling index in CGA322704-treated mice at any time point. Tif:MAGf mice: CGA322704: slightly ↓ bw, ↓ fc (wks 1–4, lesser during wks 5–8), ↓ kidney wts (1 and 20 wks), ↑ liver wts (10 and 20 wks);

Study Type/Species/PMRA No.	Study Results
PMRA No. 859927, 859928, 859933, 859934, 859935	CGA265307: slightly ↑ bw, ↑ liver wts (10 wks), ↓ median BrdU labelling index (10 wks); thiamethoxam: ↓ total protein and plasma cholesterol (all timepoints), ↓ albumin and ↑ inflammatory cell infiltration and median BrdU labelling index (20 wks), ↑ hepatocellular apoptosis (10 wks), ↓ kidney and ↑ liver wts (1, 10 and 20 wks), ↑ ALT, hepatocellular necrosis and hepatocellular hypertrophy characterized by enlarged centrilobular/ midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (10 and 20 wks). CD-1 mice: CGA322704: ↓ bw (10 animals sacrificed prematurely in wks 10 and 11), ↓ fc (wks 1–4, lesser during wks 5–8), ↓ kidney wts (1, 10 and 20 wks), ↓ liver wts (1 wk); CGA265307: ↓ kidney wts (10 wks); thiamethoxam: slightly ↓ bw, slightly ↓ plasma albumin, total protein and plasma cholesterol (all timepoints), ↑ ALT, ↓ kidney wts, ↑ hepatocellular necrosis, ↑ hepatocellular apoptosis and pigmentation, ↑ median BrdU labelling index and ↑ hepatocellular hypertrophy characterized by enlarged centrilobular/ midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (10 and 20 wks), ↑ inflammatory cell infiltration (20 wks). Similar liver toxicity was noted in 2 strains of mice; mainly attributed to thiamethoxam and not the main metabolites.
Assessment of hepatic cell proliferation, 40-wk dietary study Mice, Tif:MAG ♂ PMRA No. 859932 (Satellite study of PMRA No. 859923)	≥ 62 mg/kg bw/day: ↑ hepatocellular mitotic index (BrdU labelling index).
Role of nitric oxide in the development of hepatotoxicity, in vitro study Mice, Tif:MAG PMRA No. 859924	The metabolite CGA265307 inhibited nitric oxide synthase to a similar extent as the selective iNOS inhibitor L-NAME. Thiamethoxam and metabolites CGA322704, CGA330050, NOA421276, NOA412275, and NOA404617 were not as effective at inhibiting iNOS over a range of substrate concentrations from 0–0.5 mM.
Role of nitric oxide in the development of hepatotoxicity, dietary study Mice, Tif:MAG ♂ PMRA No. 859924	Animals received 0 or 2000 ppm CGA652307 in diet for 7 days and were then injected intraperitoneallywith 10 uL/kg CCl_4, or 0, 10 or 20 uL/kg CCl_4 alone, by injection, In vivo experiment: CGA652307: no evidence of liver toxicity. CGA652307 plus intraperitoneal injectionCCl_4: ↑ ALT (greater than animals given intraperitoneal injection CCl_4 alone), inhibition of nitric oxide synthase (similar extent as the selective iNOS inhibitor L-NAME),

Study Type/Species/PMRA No.	Study Results
	microscopic examination of the liver revealed evidence of liver toxicity (further details not available). ≥ 10 µL/kg CCl_4 intraperitoneal injection alone: slightly ↑ ALT (maximal 16 hrs post-dosing), ↑ TNFα (16 hrs post-dosing); 20 µL/kg CCl_4 intraperitoneal injection alone: ↑ ALT, ↑ serum levels of nitrite (20 hrs post-dosing). A reduction of iNOS or NO in vivo was not demonstrated in this study. There were no treatment-related mortalities or clinical signs of toxicity noted.
Determination of oxidative stress in the liver, dietary study (10, 20, 30, 40 or 50 wks) Mice, Tif:MAG ♂ PMRA No. 859921	≥ 314 mg/kg bw/day: ↓ final bw, ↑ incidence of accentuated lobular pattern of the liver correlated with hepatic fatty change (after 10, 30 and 40 wks), ↑ hepatic oxidized glutathione (after 10 and 50 wks), ↑ mean hepatic γ-glutamylcysteine synthetase activity, mean hepatic glutathione S-transferase activity, mean hepatic concentration of reduced glutathione and hepatocellular hypertrophy and necrosis characterized by enlarged centrilobular/ midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (all time points); 684 mg/kg bw/day: ↑ incidence of hepatocellular apoptosis with mainly centrilobular location, slightly ↓ mean concentration of 8-isoprostane F2α in the liver (20 wks onward), ↑ hepatic oxidized glutathione (all time points).
Assessment of hepatic cell proliferation and apoptosis, dietary study (10, 20, 30, 40 or 50 wks) Mice, Tif:MAG ♂ PMRA No. 859923	There were no treatment-related clinical signs or deaths during the study. ≥ 62 mg/kg bw/day: hepatocellular necrosis affecting single cells or small groups of cells with mainly centrilobular localization and often accompanied by inflammatory cells (wk 40 onwards), accentuated lobular pattern of the liver, inflammatory cell infiltration of the liver correlated with hepatic fatty change (wk 30 onwards), ↑ incidence and/or severity of pigmentation characterized by yellow/brown pigment granules in the cytoplasm of centrilobular hepatocytes (wk 50), ↑ median TUNEL area densities; ≥ 151 mg/kg bw/day: ↓ fc (wk 40 onward), ↑ AST (all timepoints) and ALT (all timepoints), ↑ incidence and/or severity of hepatocellular apoptosis affecting single cells or small groups of cells with mainly centrilobular localization (wks 20 and 30), ↑ median BrdU labelling index (wk 40 onwards); ≥ 314 mg/kg bw/day: ↓ bw (wk 50), ↓ fc (wk 9 onward), ↑ relative liver wt (wks 20 and 40), ↓ absolute kidney wt (wk 30 onward), ↓ relative kidney wt (wk 30 and 40), ↑ incidence of hepatocellular hypertrophy characterized by enlarged centrilobular/midzonal hepatocytes with ↑ amounts of cytoplasmic glycogen, fat and SER (wk 30 onward);

Study Type/Species/PMRA No.	Study Results
	684 mg/kg bw/day: ↑ relative liver wt (wk 10 onward), ↓ absolute kidney wt (wk 10 onward), ↓ absolute spleen wt (wk 40), ↑ relative testis wt (wks 20 and 40).
Comparative hepatotoxicity of metabolites in two species of animals, dietary study Mice, Tif:MAG ♂; Rats, Tif:RAIf ♀ PMRA No. 859926	Study 1 (PMRA No. 859927, 859928, 859933, 859934, 859935): 2500 ppm thiamethoxam (~ 314 mg/kg bw/day), 2000 ppm CGA322704 or 500 ppm CGA265307 in ♂ mice for 1, 10 or 20 wks. 314 mg/kg bw/day thiamethoxam: ↓ plasma cholesterol and serum protein (wk 1 onward), ↑ ALT and hepatocellular hypertrophy, necrosis and apoptosis (wk 10 onwards), ↑ AST, inflammatory cell infiltration and pigmentation in the liver and hepatic cell replication rates (wk 20). CGA322704 and CGA265307: no evidence of liver toxicity. Study 2 - CGA330050: 0, 500 or 1000 ppm CGA330050 in ♂ mice for 1 or 10 wks ≥ 500 ppm: similar toxicity to mice dosed with thiamethoxam in Study 1 (↓ plasma cholesterol (4 and 10 wks); 1000 ppm: similar toxicity to mice dosed with thiamethoxam in Study 1 (↓ total protein (4 and 10 wks), ↑ hepatocyte hypertrophy characterised by enlarged, pale-staining centrilobular hepatocytes with a floccular or microvesicular cytoplasm, apoptotic hepatocytes showing single cell necrosis and ↑ cell replication rates (S-phase) in the liver (10 wks)). Study 3 - CGA330050: 0, 500 or 1000 ppm CGA330050 in ♀ rats for 1 wk ≥ 500 ppm: ↓ plasma cholesterol, ↑ ALT and AST, No effect on liver wt.
Assessment of replicative DNA synthesis, 28-day dietary study Rats, Tif:RAIf ♂ PMRA No. 1178139	Immunohistochemical staining of liver sections from control and high-dose (~711 mg/kg bw/day) ♂ for proliferating cell nuclear antigen gave no indication of a treatment-related ↑ in the fraction of DNA-synthesizing hepatocytes in S-phase.
Investigation of induction of liver enzymes, 10-wk dietary study Rats, Tif:RAIf ♀ PMRA No. 859922	No treatment-related effects noted on the liver protein content or levels of cytochrome P450, 7-ethoxy, 7-pentoxy and 7-benzyloxyresorufin-O-dealkylase, coumarin 7-hydroxylase, testosterone hydroxylation, lauric acid 11 and 12-hydroxylation, UDP-glucuronosyltransferase, reduced and oxidized glutathione or cytosolic γ-glutamylcysteine synthetase following exposure to thiamethoxam. ≥ 59 mg/kg bw/day: slightly ↓ activity of liver microsomal methoxyresorufin O-demethylase (1 wk); 180 mg/kg bw/day: slightly ↑ activity of liver cytosolic glutathione S-transferase, microsomal epoxide hydrolase and peroxisomal β-oxidation (10 wks).
Assessment of hepatic cell proliferation and apoptosis, up to 50 wks dietary study	No treatment-related effects in clinical chemistry, urinalysis, organ weights, histopathology, hepatocyte proliferation, cell turn over or apoptosis noted in this study.

Study Type/Species/PMRA No.	Study Results
Rats, Tif:RAIf ♀ PMRA No. 859929, 859930, 859931	≥ 59 mg/kg bw/day: ↑ urinary volume (first 11 wks), significant ↑ in urinary pH (wk 11), ↓ mononuclear hepatocyte S-phase (up to 31 wks); 180 mg/kg bw/day: ↑ hunched posture or clinical signs of morbidity prior to sacrifice, ↑ mortality rate (up to 30 wks), ↓ bw, bwg and fc (first 3 wks), ↓ fc (first 13 wks), significant ↓ in urinary pH (21 to 42 wks), ↑ incidence of kidney lesions (dilated pelvis, enlarged, pale, roughened surface or discoloured), spleen (reduced size, pale), urinary bladder (distended, bloody urine) and thymus (small), ↓ mononuclear hepatocyte S-phase (11, 31, 41 and 51 wks), ↓ total number of apoptotic bodies (2 wks). Thiamethoxam treatment for up to 50 wks did not demonstrate specific toxicological effects in the livers of rats.
Summary of cholesterol data from various studies to identify patterns of effect which could be correlated with occurrence of tumours in long-term studies, dietary studies Mice, Tif:MAG and CD-1; Rats, Tif:RAIf PMRA No. 859895	<u>50 wk dietary study in mice (PMRA No. 859923)</u>: A dose-dependent ↓ in plasma cholesterol levels starting at 500 ppm from 10 wks onward. <u>7-day dietary study in mice:</u> ↓ plasma cholesterol levels after 1, 4 and 7 daily doses and ↓ HDL and LDL after 4 and 7 daily doses of 350 mg/kg bw/day. <u>20-wk dietary study of thiamethoxam and its metabolites in 2 strains of mice (PMRA Nos. 859927, 859928, 859933, 859934, 859935)</u>: ↓ cholesterol in both strains of mice at 2500 ppm for 1, 10 and 20 wks. Neither CGA322704 nor CGA265307 altered plasma cholesterol levels. <u>50-wk dietary study in rats (PMRA No. 859929, 859930, 859931)</u>: No treatment-related alterations in cholesterol levels in rats fed diets containing 0, 1000 or 3000 ppm for 1, 10, 20, 30, 40 or 50 wks. <u>10-wk CGA330050 dietary study in mice (PMRA No. 859926)</u>: Mice fed diets containing CGA330050 had ↓ plasma cholesterol following exposure to 500 and 1000 ppm for 1, 4 and 10 wks. <u>4-wk dietary study with 2 wk recovery in mice:</u> ↓ plasma cholesterol levels after 2500 ppm for 4 wks, recovery noted after 2 wks of control diet. <u>HMG-CoA reductase activity in mice - in vitro:</u> Neither thiamethoxam nor its metabolites inhibited the HMG-CoA reductase mediated-metabolism of HMG-CoA to mevalonate. <u>HMG-CoA reductase activity in mice - in vivo</u>: Administration of 2500 ppm in the diet for 20 wks did not affect HMG-CoA reductase activity. <u>3H-Mevalonate incorporation in mice - in vivo</u>: No treatment-related alterations in cholesterol after 5000 ppm for 7 days whereas the level of squalene was ~4-fold ↑ in the livers from mice fed

Study Type/Species/PMRA No.	Study Results
	thiamethoxam compared to control animals.

Table 4 Toxicity Profile of End-Use Products (Actara 240SC Insecticide and Actara 25WG Insecticide)

Study Type/Animal/PMRA No.	Study Results
Actara 240SC	
Acute oral Rat (Sprague-Dawley) PMRA No. 860838	LD50 (♂/♀) > 5000 mg/kg bw Tremors 2 ♂ day of dosing; squinting of eyes, hypoactivity, staggered gait in 1 of these animals. Red-stained face in 1 ♀ within hrs of dosing. All normal by day 1. Low toxicity.
Acute dermal Rabbit (New Zealand White) PMRA No. 860839	LD_{50} (♂/♀) > 2000 mg/kg bw Low toxicity.
Acute inhalation Rat (Sprague-Dawley) PMRA No. 860840	LC_{50} (♂/♀) > 0.641 mg/L The MMAD for the 2.67 mg/L concentration was too high (>4µm), indicating that the test substance did not reach the alveolar tissue; therefore, only the low dose concentration (0.641 mg/L) could be considered. Slight toxicity.
Skin irritation Rabbit (New Zealand White) PMRA No. 860842	MAS = 0.17 MIS = 0.67 (4 hrs) Slightly irritating.
Eye irritation Rabbit (New Zealand White) PMRA No. 860841	MAS = 0 MIS = 4 Non-irritating.
Skin sensitization (Buehler) Guinea Pig (Hartley) PMRA No. 801043	Not a dermal sensitizer.
Actara 25WG	

Study Type/Animal/PMRA No.	Study Results
Acute oral Rat (Sprague-Dawley) PMRA No. 861041	LD_{50} (♂/♀) > 5000 mg/kg bw Clinical signs of toxicity, including hypoactivity, staggered gait, tremors, mydriasis, hunched posture and squinting of the eyes were recorded in all test animals on the day of treatment. All animals resumed a normal appearance from day 1. Low toxicity.
Acute dermal Rabbit (New Zealand White) PMRA No. 861042	LD_{50} (♂/♀) > 2000 mg/kg bw Low toxicity.
Acute inhalation Rat (Sprague-Dawley) PMRA No. 861043	LC_{50} > 2.79 mg/L Low toxicity.
Skin irritation Rabbit (New Zealand White) PMRA No. 861045	MAS = 1.3 MIS = 1.7 (4 hr) Slightly irritating.
Eye irritation Rabbit (New Zealand White) PMRA No. 861044	MAS = 5.6 MIS = 24.8 (1 hr) Mildly irritating.
Skin sensitization (Buehler) Guinea Pig (Hartley) PMRA No. 861046	 Not a dermal sensitizer.

Table 5 Toxicology Reference Values for Use in Human Health Risk Assessment for Thiamethoxam

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary - general population	Developmental neurotoxicity study in rats	NOAEL = 35 mg/kg bw/day Brain wt reductions and morphometric changes	300
	ARfD = 0.1 mg/kg bw		
Repeated dietary - general population	Combined results of 2-generation reproductive toxicity studies in rats	NOAEL = 1.2 mg/kg bw/day Testicular and sperm toxicity	300
	ADI = 0.004 mg/kg bw/day		

Short, intermediate and long-term dermal[2]	Combined results of 2-generation reproductive toxicity studies in rats	NOAEL = 1.2 mg/kg bw/day Testicular and sperm toxicity	300
Short, intermediate and long-term inhalation[3]	Combined results of 2-generation reproductive toxicity studies in rats	NOAEL = 1.2 mg/kg bw/day Testicular and sperm toxicity	300
Cancer	Not genotoxic and not oncogenic in rats. Liver tumors in mice linked to the greater ability of the mouse, compared to humans and rats, to metabolize thiamethoxam to a hepatotoxic metabolite; threshold approach to cancer risk assessment taken.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target margin of exposure for occupational assessments

[2] Since an oral NOAEL was selected, a dermal absorption factor was used in route-to-route extrapolation

[3] Since an oral NOAEL was selected, an inhalation absorption factor of 100% (default value) was used in route-to-route extrapolation.

Table 6 Mixer/Loader/Applicator Risk Assessment

Scenario	Equipment	Dermal Exposure (mg/kg bw/day)[a]	Inhalation Exposure (mg/kg bw/day)[b]	Total Exposure (mg/kg bw/day)	MOE[c]
Farmer Mixer/Loader/Applicator	Groundboom	0.00014	0.00006	0.0002	5983
Custom Mixer/Loader	Groundboom	0.00048	0.00011	0.00057	2107
Custom Applicator	Groundboom	0.00009	0.00011	0.0002	6050
Farmer& Custom Mixer/Loader/Applicator	Airblast	0.00055	0.00015	0.0007	1723
Farmer Mixer/Loader/Applicator	In-furrow Groundboom	0.00028	0.00034	0.00062	1942
Custom Mixer/Loader	In-furrow Groundboom	0.00064	0.0008	0.00144	831
Custom Applicator	In-furrow Groundboom	0.00041	0.00048	0.00089	1344

[a] Where exposure mg/kg/day = maximum rate * area treated per day * unit exposure * dermal absorption *conversion factor (1/1000 mg/µg)/70 kg bw.
[b] Where exposure mg/kg/day = maximum rate * area treated per day * unit exposure * conversion factor (1/1000 mg/µg) / 70 kg bw.
[c] Where MOE = NOAEL/Total Exposure; the MOE is based on a NOAEL of 1.2 mg/kg bw/day from a rat reproduction study. The target MOE is 300.

Table 7 Post-application Risk Assessment – Pome Fruit Orchards

Scenarios	Transfer Coefficient[a] (cm^2/hr)	DFR (µg/cm^2)	Dermal Exposure[b] (mg/kg bw/day)	MOE[c]
Pruning, Scouting	500	0.283	0.0004	2968
Handline irrigation	1100	0.283	0.00089	1349
Hand harvesting	11500	0.283	0.0012	989
Thinning	3000	0.283	0.0024	495

[a] Transfer Coefficients, based on ARTF data. The applicant, Syngenta Crop Protection Canada, is a member of ARTF.
[b] Exposure estimates were calculated using the following formula:
DFR Value (µg/cm^2) × Transfer Coefficient (cm^2/hr) × Hours Worked per Day (hr) × Conversion Factor (1mg/1000µg)/Body Weight (70 kg)
[c] Based on a NOAEL of 1.2 mg/kg bw/day from a rat reproduction study. The target MOE is 300.

Table 8. Integrated Food Residue Chemistry Summary

NATURE OF THE RESIDUE IN PLANTS PEAR		
Radiolabel position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labelled at the 4-position) rings	
Test site	Orchard	
Treatment	Foliar application	
Rate	150 or 1500 g a.i./ha	
Seasonal rate	300 or 3000 g a.i./ha	
PHI	15 days	
Most of the radioactivity remained on the foliage. Most of the radioactivity on the fruit was removed with a surface wash of acetonitrile.		
Metabolites identified	**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**
Pear fruit	Thiamethoxam, CGA 322704	CGA 322704 glucose conjugate, CGA 353968, Desmethyl-CGA 353968, CGA 265307, CGA 355190, NOA 407475, CGA 349208, NOA 405217, CGA 382191, NOA 421275
NATURE OF THE RESIDUE IN PLANTS POTATO		
Radiolabel position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labeled at the 4-position) rings	
Test site	Outdoor field plots	
Treatment	Seed treatment	
Rate	6.1 or 6.3 g/100 kg seed and 26.4 or 33.4 g/100 kg seed	
Seasonal rate	6.1 or 6.3 g/100 kg seed and 26.4 or 33.4 g/100 kg seed	
PHI	84 and 106 days	
Total residues were substantially higher in foliage than tubers, suggested translocation of residues to foliar tissue during plant growth.		
Metabolites identified	**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**
Potato tuber	Thiamethoxam	CGA 322704, CGA 322704 glucose conjugate, CGA 353968, Desmethyl-CGA 353968, CGA 265307, CGA 355190, CGA 340575, CGA 282149, CGA 353042, NOA 407475, CGA 349208, NOA 405217, CGA 382191, NOA 421275, NOA 421276, NOA 436944, N-Glucoside of CGA 353968, Glucoside of CGA 349208, Hydroxylamine Glucoside of NOA 421276, Malonyl Glucoside of CGA 349208

CONFINED ROTATIONAL CROP STUDY Turnips, mustard (spinach), wheat			
Radiolabel position		^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labeled at the 4-position) rings	
Test Site		Separate plots	
Formulation used for trial		Not specified	
Application rate and timing		100 (Study 1) or 200 g a.i./ha (Study 2) applied to bare soil 30, 120 and 365 days before seeding rotational crops	
Metabolites identified		**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**
Radiolabel Position		^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labeled at the 4-position) rings	
Study 1			
Turnips	PBI 30	Thiamethoxam, CGA 322704	CGA 353968
	PBI 120	Thiamethoxam, CGA 322704, CGA 359683	CGA 353968
	PBI 365	Thiamethoxam, CGA 322704, CGA 359683	None
Mustard	PBI 30	Thiamethoxam, CGA 322704	CGA 265307, CGA 353968, CGA 359683
	PBI 120	Thiamethoxam, CGA 322704, CGA 353968	None
Spinach	PBI 365	CGA 322704	Thiamethoxam, CGA 265307, CGA 353968, CGA 359683
Wheat	PBI 30	Thiamethoxam, CGA 322704, CGA 265307	CGA 353968, CGA 355190, Desmethyl-CGA 353968
	PBI 120	Thiamethoxam, CGA 322704, CGA 265307	CGA 353968
	PBI 365	CGA 322704, CGA 359683	CGA 265307, Desmethyl-CGA 353968
Study 2			
Lettuce	PBI 30	Thiamethoxam, CGA 322704, NOA 405217	NOA 407475, NOA 421275, CGA 382191
	PBI 120	Thiamethoxam, CGA 322704	None
	PBI 365	Not analyzed	Not analyzed
Radish	PBI 30	Thiamethoxam, CGA 322704	CGA 322704, NOA 407475, NOA 421275, CGA 265307, CGA 353968, Desmethyl-CGA 353968, CGA 355190, CGA 382191
	PBI 120	None	Thiamethoxam, CGA 322704, CGA 265307
	PBI 365	Not analyzed	Not analyzed
Spring wheat		CGA 322704, NOA 421275	Thiamethoxam, CGA 322704, CGA 265307, NOA 407475, NOA 421275, Desmethyl-CGA 353968
	PBI 120	CGA 322704	Thiamethoxam, CGA 322704, CGA 265307, NOA 421275, NOA 407475, NOA 405217, CGA 382191, Desmethyl-CGA 353968

PBI 365	None	CGA 322704, CGA 265307	
NATURE OF THE RESIDUE IN LAYING HEN			
Species	Dose Level	Length of Dosing (d)	Sacrifice
Hen	97.6 or 111 mg/kg/day once daily	3	6 hours after last dose
Of the total radioactive dose, approximately 80% was excreted in the urine and faeces, 0.1% was secreted in the eggs. Radioactivity remaining in edible tissues accounted for 1.3–1.5% of the dose.			
Metabolites identified	**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**	
Radiolabel Position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labeled at the 4-position) rings		
Egg white	CGA 322704, CGA 265307, NOA 404617	Thiamethoxam, NOA 404617, Desmethyl-CGA 353968, NOA 405217, CGA 355190, 8U	
Egg yolk	Thiamethoxam, CGA 322704, CGA 265307	NOA 407475, NOA 405217, NOA 421275, 8U	
Liver	CGA 322704, CGA 265307, NOA 421275, MU3	Thiamethoxam, Desmethyl-CGA 353968, NOA 402988, NOA 405217, NOA 404617, NOA 421275, 8U	
Muscle	Thiamethoxam, NOA 421275, MU3	CGA 322704, NOA 407475, CGA 265307, NOA 405217, NOA 421275, CGA 355190, 8U	
Skin/fat	Thiamethoxam, CGA 265307	CGA 322704, NOA 407475, NOA 421275, NOA 404617, MU3, Desmethyl-CGA 353968, 8U, CGA 355190	
NATURE OF THE RESIDUE IN RUMINANT			
Species	Dose Level	Length of Dosing (d)	Sacrifice
Goat (lactating)	100.6 or 111.9 ppm once daily	3	6 hours after the last dose
For both ^{14}C test substances, the dosed radioactivity was eliminated primarily in the urine (44–49%) and faeces (8–12%). Approximately 1% was secreted in the milk. Radioactivity remaining in edible tissues at sacrifice accounted for 3.4–3.7% of the dose. Minor amounts of radioactivity (0.6%) were detected in blood and bile and 18–26% was present in the gastrointestinal tract and rumen at sacrifice.			
Metabolites identified	**Major metabolites (>10% TRRs)**	**Minor metabolites (<10% TRRs)**	
Radiolabel Position	^{14}C-thiazole (label at the 2-position) or ^{14}C-oxadiazine (labeled at the 4-position) rings		
Milk	Thiamethoxam, CGA 322704, CGA 265307	Desmethyl-CGA 353968, NOA 405217	
Liver	NOA 407475, NOA 421275, NOA 421276, L14	Thiamethoxam, CGA 322704, CGA 265307, NOA 404617, MU12, Desmethyl-CGA 353968, CGA 355190, CGA 353968, CGA 309335, CGA 359683, N5, NOA	

		405217
Kidney	Thiamethoxam, NOA 421275, NOA 421276, N5	CGA 322704, NOA 407475, CGA 265307, NOA 404617, L14, MU12, Desmethyl-CGA 353968, CGA 355190, CGA 353968, CGA 359683, NOA 405217
Muscle	Thiamethoxam, NOA 421276, MU12	CGA 322704, NOA 407475, CGA 265307, NOA 421275, NOA 421276, L14, MU12, Desmethyl-CGA 353968, NOA 405217
Fat	Thiamethoxam, CGA 322704, NOA 421275, NOA 421276	CGA 265307, NOA 404617, Desmethyl-CGA 353968, NOA 405217, MU12

CROP FIELD TRIALS APPLES

Eight field trials were conducted throughout Canada (1, 1A, 5, 5B and 11) during the 2002 growing season. The number and location of the field trials are in accordance with the *Residue Chemistry Guidelines* (DIR98-02). Apples were treated with 79 g a.i./ha or 192 g a.i./ha; 0.4H or 1.0H the proposed Canadian rate, respectively.

Commodity	Total Rate g a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	SDEV
Apple fruit	79	110–154	Thiamethoxam + CGA 322704	16	< 0.02	< 0.02	< 0.02	< 0.02/ 0.02	N/A
	192	35		2	NQ (0.016)	NQ (0.020)	NQ (0.018)	NQ (0.018)/ 0.02	N/A
	192	59–61		16	NQ (0.013)	< 0.02	< 0.02	NQ (0.017)/ 0.02	0.003
	192	66–114		22	< 0.02	< 0.02	< 0.02	< 0.02	N/A

CROP FIELD TRIALS PEARS

Five field trials were conducted throughout Canada (1A, 5 and 11) during the 2002 growing season. The number and location of the field trials are in accordance with the *Residue Chemistry Guidelines* (DIR98-02). Pears were treated with 79 g a.i./ha or 192 g a.i./ha; 0.4H or 1.0H the proposed Canadian rate, respectively.

Commodity	Total Rate g	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/	SDEV

	a.i./ha							Media n	
Pear fruit	79	97–147	Thiamethoxam + CGA 322704	10	< 0.02	< 0.02	< 0.02	<0.02/ 0.02	N/A
	192	59–61		8	NQ (0.008)	< 0.02	< 0.02	NQ (0.016)/ 0.02	0.005
	192	67–109		10	NQ (0.014)	< 0.02	< 0.02	NQ (0.017)/ 0.02	0.003

CROP FIELD TRIALS POTATOES

Twelve field trials were conducted throughout Canada (1, 1A, 5, 5A, 5B, 7A, 12 and 14) during the 2002 growing season. The location of the field trials are in accordance with the *Residue Chemistry Guidelines* (DIR98-02). Potatoes were treated with either an in-furrow 116 g a.i./ha application or a foliar 52 g a.i./ha application; 1.0H the proposed Canadian rate.

Commodity	Total Rate g a.i./ha	PHI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	SDEV
Potato tubers	116	79–106	Thiamethoxam + CGA 322704	24	NQ (0.007)	0.022	0.021	NQ (0.014)/ 0.02	0.004
	52	3		2	< 0.02	< 0.02	< 0.02	<0.02/ 0.02	N/A
	52	7–8		24	NQ (0.013)	< 0.02	< 0.02	0.020/ 0.02	0.002
	52	9–11		24	< 0.02	< 0.02	< 0.02	<0.02/ 0.02	N/A
	52	13–15		24	NQ (0.008)	< 0.02	< 0.02	NQ (0.019)/ 0.02	0.003
	52	21		2	< 0.02	< 0.02	< 0.02	< 0.02/ 0.02	N/A

RESIDUE DECLINE APPLES AND POTATOES

Residue decline studies were conducted on apple and potatoes. In both studies, thiamethoxam residue data was less than the combined LOQ (0.02 ppm; thiamethoxam + CGA 322704) when trials were conducted at GAP. No residue decline information could be obtained when apple or potato samples were harvested at or near the proposed preharvest interval.

FIELD ACCUMULATION IN ROTATIONAL CROPS WHEAT, LETTUCE, TURNIPS

Rotational field trials were conducted in Fresno County, California, Indian River County, Florida and Champaign County, Illinois on soil textures ranging from sand to silty clay loam. Peppers, leaf lettuce and mustard greens were planted as primary crops. At each test site, thiamethoxam was applied to the primary crop as an in-furrow application at planting (leaf lettuce and mustard greens) or as a transplant

drench (peppers) followed by a broadcast foliar application 30 to 51 days later for a seasonal application of ~200 g a.i./ha. At each test site, control and treated plots were planted with leaf lettuce, turnips and wheat as representative rotational crops at PBIs of approximately 30, 120 and 180 days after the final application of thiamethoxam.

Commodity	Total Rate g a.i./ha	PBI (days)	Analyte	Residue Levels (ppm)					
				n	Min.	Max.	HAFT	Mean/ Median	SDEV
Wheat forage	200	30	Thiamethoxam + CGA 322704	2	0.04	0.04	0.04	0.04/0.04	N/A
		120		3	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A
Wheat hay		30		2	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A
		120		3	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A
Lettuce		30		2	< 0.02	< 0.02	< 0.02	< 0.02/<	N/A
		120		3	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A
Turnip tops		30		2	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A
		120		3	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A
Turnip roots		30		2	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A
		120		3	< 0.02	< 0.02	< 0.02	< 0.02/< 0.02	N/A

PROCESSED FOOD AND FEED APPLES AND POTATOES

Fraction	Mean Residue Levels (ppm)	Concentration factor
Apple RAC (291 g a.i./ha)	0.09	N/A
Wet apple pomace (291 g a.i./ha)	0.12	1.6
Apple juice (291 g a.i./ha)	0.08	0.75
Potato tubers RAC (571 g a.i./ha)	0.03	N/A
Potato culls (571 g a.i./ha)	0.05	1.2
Potato wet peel and trimmings (571 g a.i./ha)	0.03	1.0
Potato granules (571 g a.i./ha)	0.04	1.2
Potato chips (571 g a.i./ha)	0.03	1.9

LIVESTOCK FEEDING

Soybean, potato, apples, wheat, barley, canola and corn are the feed items on the Canadian label. Poultry feed items on the Canadian label include corn, canola and barley and swine feed items include potato and barley. The estimated MTDB is 0.16 ppm for beef cattle, 0.10 ppm for dairy cattle, 0.02 ppm for poultry

and 0.02 ppm for swine.			
Tissues/Matrices	Feeding level	Mean residue levels (ppm)	Anticipated residues (ppm)
Whole milk	2	0.012	0.0006
	6	0.045	0.0008
	20	0.160	0.0008
Beef kidney	2	< 0.02	< 0.02
	6	< 0.02	< 0.02
	20	0.036	0.0003
Beef liver	2	0.055	0.0044
	6	0.148	0.0004
	20	0.326	0.0026
Meat	2	< 0.02	< 0.02
	6	< 0.02	< 0.02
	20	0.045	0.0004

Table 9 Food Residue Chemistry Overview of Metabolism Studies and Risk Assessment

PLANT STUDIES			
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT **Primary Crops** **Rotational Crops**	The sum of thiamethoxam and CGA 322704		
METABOLIC PROFILE IN DIVERSE CROPS	Similar in five diverse crops (corn, cucumber, pear, potato and lettuce)		
ANIMAL STUDIES - Poultry and Ruminant			
RESIDUE DEFINITION FOR ENFORCEMENT AND RISK ASSESSMENT	The sum of thiamethoxam and CGA 322704		
METABOLIC PROFILE IN ANIMALS	Quantitative and qualitative differences in poultry and ruminants, but does not affect overall profile assessment.		
FAT SOLUBLE RESIDUE	NO, based on Log K_{ow} = -0.13		
DIETARY RISK from food and water			
Chronic Dietary Risk **ADI = 0.004 mg/kg bw** **PGW water number**	**POPULATION**	**ESTIMATED RISK (% of ADI)**	
		Intermediate Food	**Intermediate Food + Water**
	All infants < 1 yr old	17.7	20.3

= 1.516 µg/L Refined includes STMRs, experimental or default processing factors	Children 1 to 2 yrs	25.6	26.8
	Children 3 to 5 yrs	19.6	20.7
	Children 6 to 12 yrs	10.6	11.4
	Youth 13 to 19 yrs	5.7	6.2
	Adults 20 to 49 yrs	4.7	5.5
	Adults 50+ yrs	5.0	5.8
	Females 13 to 49 yrs	4.8	5.6
	Total Population	7.1	7.9
Acute Dietary Exposure Analysis, 95th percentile EEC = 7.19 µg/L (level 2)	POPULATION	ESTIMATED RISK (% of ARfD)	
		Basic Food	Basic Food + Water
ARfD = 0.115 mg/kg bw Basic includes MRLs and US tolerances, experimental or default processing factors	All infants < 1 yr old	9.05	9.43
	Children 1 to 2 yrs	10.25	10.36
	Children 3 to 5 yrs	7.97	8.19
	Children 6 to 12 yrs	4.90	5.09
	Youth 13 to 19 yrs	2.87	3.01
	Adults 20 to 49 yrs	2.42	2.59
	Adults 50 + yrs	2.36	2.52
	Females 13 to 49 yrs	2.41	2.57
	Total Population	3.82	3.97

Table 10 Fate and Behaviour in the Environment
Refer to PRVD2017-24, PSRD2018-02, and ERC2007-01

Table 11 Toxicity to Non-Target Species
Refer to PRVD2017-24, PSRD2018-02, and ERC2007-01

Appendix II

Subsequent to the publication of ERC2007-01, the major new uses of Ornamentals Outdoor (USC 27) and Greenhouse Food Crops (USC 5) were added to Thiamethoxam Technical, in 2010 and 2012 respectively. These use expansions were received under User Requested Minor Use Label Expansion (URMULE) applications, and were therefore not subject to public consultation. The evaluation for these two use expansions are summarized below.

1. USC 27 (Ornamentals Outdoor)

The purpose of this application was to amend the registration of Actara 25WG Insecticide to include the claim of control of the viburnum leaf beetle, *Pyrrhalta viburni* (Coleoptera: Chrysomelidae) on viburnum in outdoor nurseries and landscape.

Since there was no change to product chemistry and toxicological profile, assessments for chemistry and toxicology were not required. For occupational exposure, Actara 25WG Insecticide was assessed for use on ornamentals outdoor. Exposure for mixing/loading and applying Actara 25WG Insecticide to viburnum was estimated using PHED version 1.1. Risks to handlers wearing long sleeves, long pants and gloves are not of concern.

There is potential for post application exposure to workers re-entering treated nursery areas, and for bystanders and homeowners re-entering treated landscape or residential areas. Risk estimates for workers and bystanders were estimated using default assumptions for dislodgeable foliar residues. Risks to re-entry workers and bystanders re-entering treated areas on the day of application are not of concern. A food residue assessment was not required since no food uses were requested under this application.

The foliar use rate on viburnum (280 g product/ha applied one time) is lower than the maximum foliar use rate on pome fruit (385 g product/ha applied twice for a total seasonal maximum of 770 g product/ha). An increased risk to the environment was not expected as a result of this use expansion and a revised risk assessment was not conducted. Label statements were amended in accordance with current practice. The existing environmental data requirements previously identified as conditions of registration were maintained.

The use of Actara 25 WG Insecticide for control of viburnum leaf beetle (*Pyrrhalta viburni*) on viburnum in outdoor nurseries and landscape at the rate of 280 g product/ha can be supported based on the submitted efficacy data. The volume of water used should achieve thorough and uniform coverage.

In conclusion, the PMRA found the information sufficient to amend the registration of Actara 25WG Insecticide to include the claim of control of viburnum leaf beetle, *Pyrrhalta viburni* (Coleoptera: Chrysomelidae) on viburnum in Canada.

In 2014, following the registration of Flagship Insecticide, Reg. No. 30723, the use of Actara 25WG Insecticide on viburnum was removed from the label.

2. USC 5 (Greenhouse food crops)

The purpose of this application was to amend the registration of Actara 25WG Insecticide to include the use of this product against pepper weevil on greenhouse peppers. The product was already registered for the control of insect pests on potatoes, pome fruit, fruiting vegetables, bushberries, leafy vegetables (except Brassica vegetables), field peppers and viburnum.

Since there was no change to product chemistry and toxicological profile, assessments for chemistry and toxicology were not required. For occupational exposure, it was determined that the use of thiamethoxam on greenhouse peppers was not expected to result in unacceptable risks to chemical handlers and post-application re-entry workers provided the product is used according to the label directions.

To support the use expansion to greenhouse peppers, residue data from supervised residue trials conducted in Europe were reviewed, in which greenhouse sweet bell peppers were treated with thiamethoxam and harvested at PHIs of 0–1 day. Following the review of the available data, and based on the OECD MRL Calculator, it was determined that a maximum residue limit (MRL) of 0.6 ppm for residues of thiamethoxam and the CGA-322704 metabolite in/on bell peppers was considered adequate to cover residues in/on greenhouse peppers. Based on the residue data and the MRL statistical methodology, the MRL in the table below was established. Residues of thiamethoxam and CGA-322704 in bell peppers at the established MRL will not pose an unacceptable risk to any segment of the population, including infants, children, adults and seniors.

Commodity	Application Method/ Total Application Rate (g a.i./ha)	PHI (days)	Residues (ppm)		Recommended MRL (ppm)
			Min	Max	
Greenhouse Sweet Bell Peppers	Foliar/200	0–1	< 0.09	< 0.33	0.6 (bell peppers)

It was also determined that no additional environmental data were required for the proposed label expansion to greenhouse peppers. Label statements were amended in accordance with current practice and for consistency with the currently approved label. Greenhouse-specific label statements were also added. The existing environmental data requirements previously identified as conditions of registration were maintained.

The value assessment supported a label claim of suppression and, in order to achieve optimal control of pepper weevil, the use of Actara 25WG Insecticide as part of an integrated pest management (IPM) program. Efficacy data from four field trials demonstrated that Actara 25WG Insecticide can substantially reduce populations of pepper weevils and the resulting damage to pepper crops.

In conclusion, the PMRA found the information sufficient to amend the registration of Actara 25WG Insecticide to include the claim of suppression of pepper weevil on greenhouse peppers.

In 2014, following the registration of Flagship Insecticide, Reg. No. 30723, this use was removed from the Actara 25WG Insecticide label.

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

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3.0 Environment

Refer to PRVD2017-24, PSRD2018-02, and ERC2007-01 for the references. In addition, the following information was used.

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4.0 Value

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B. ADDITIONAL INFORMATION CONSIDERED

i) Published Information

Environment

Refer to PRVD2017-24 and PSRD2018-02.

ii) Unpublished Information

Environment

Refer to PRVD2017-24 and PSRD2018-02.